VOLUME 103 • MAY 1959 • NUMBER 5

INTERNAL MEDICINE

Announcement
Paul S. Rhoads

Joint Responsibility
William B. Bean

Functional Types of Acute Renal Failure and Their Early Diagnosis
William H. Waugh

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Blood Cholesterol and Uric Acid of Healthy Medical Students Under the Stress of an Examination
F. Dreyfuss and J. W. Czaczkes

Nocardia Asteroides Infection
Martha C. Larsen, Henry D. Diamond, and Harvey S. Collins

Carbohydrate Metabolism in Brain Disease
XI. Effects of Thioctic (Alpha-Lipoic) Acid in Chronic Schizophrenia
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XII. Effects of Epinephrine on Intermediary Carbohydrate Metabolism in Normal and Schizophrenic Subjects
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II. Laennec's Cirrhosis of the Liver
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Hyperthyroidism and Parkinsonism
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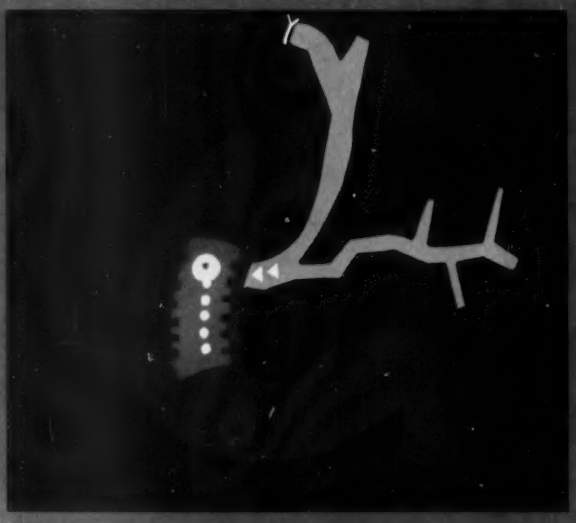

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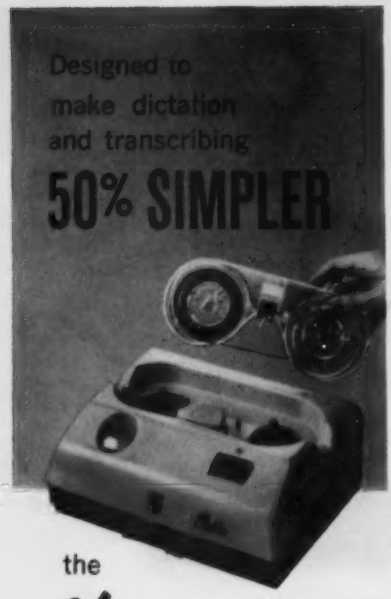

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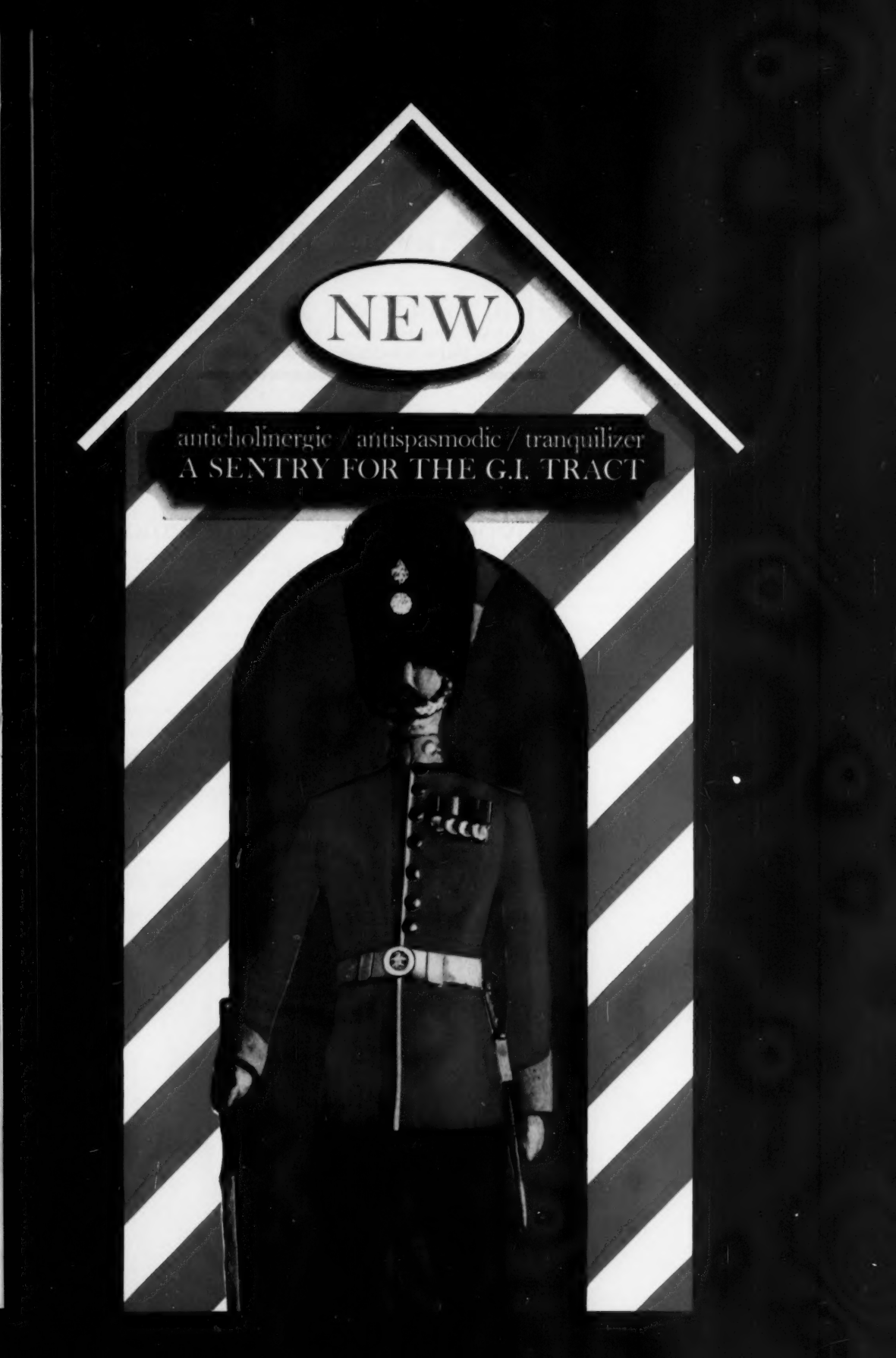
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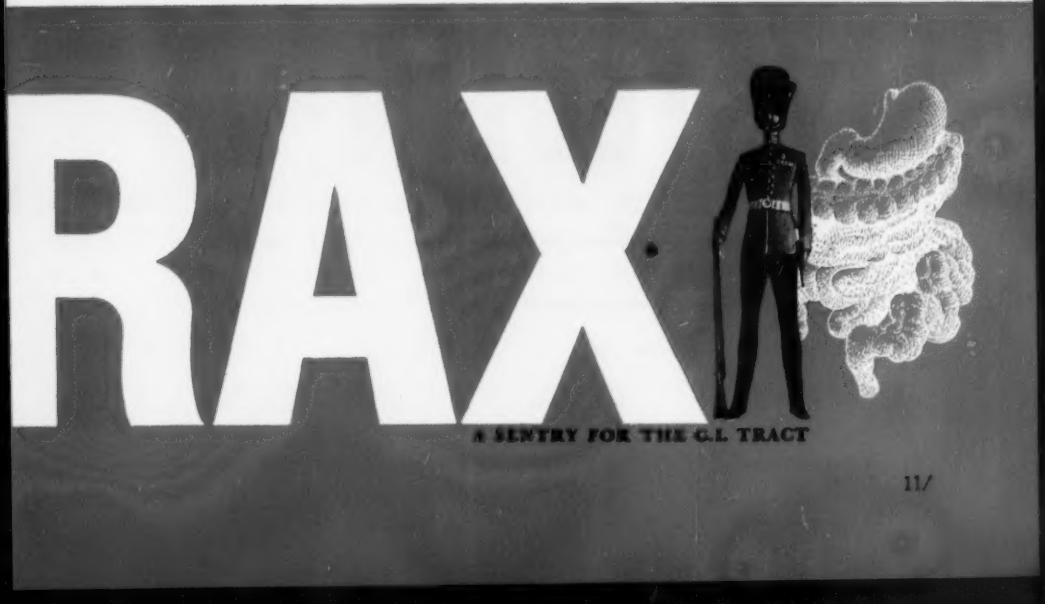

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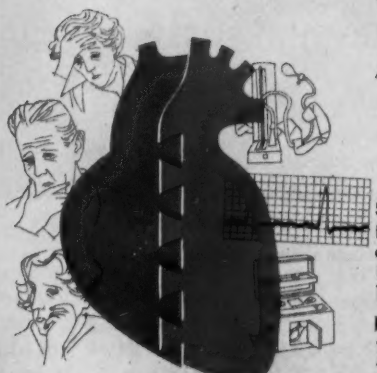

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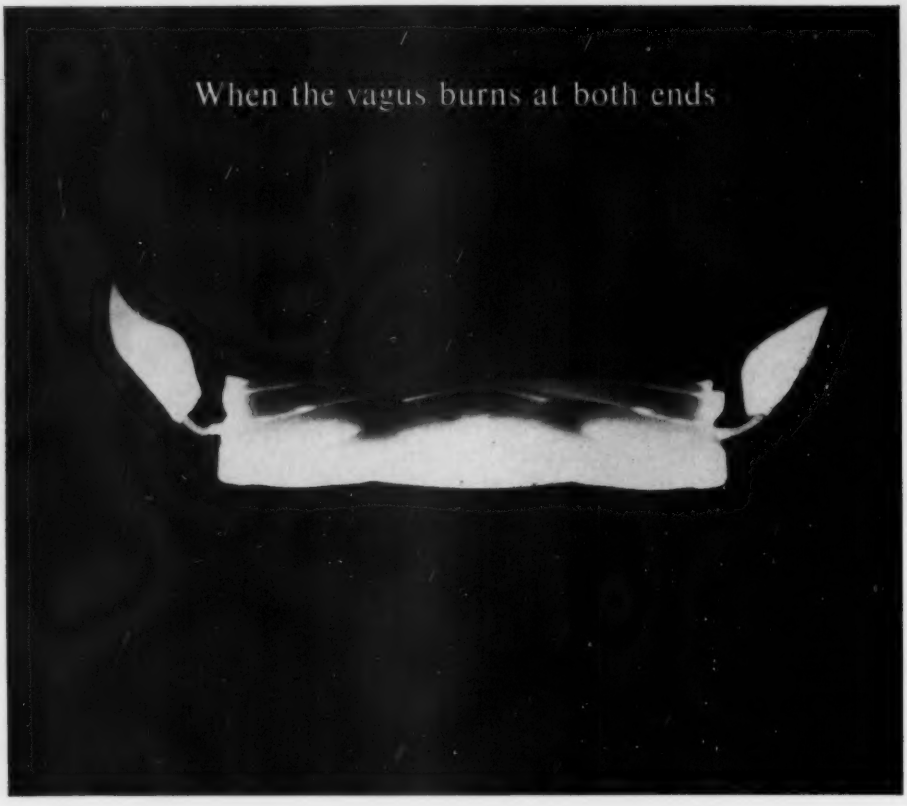

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A.M.A. ARCHIVES OF
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Editorials

Announcement

With sincere regret the ARCHIVES announces the resignation of Dr. Bruce K. Wiseman, of Columbus, Ohio, from the Editorial Board. His many friends will be happy to learn that the condition of his health, which prompted the resignation, already has considerably improved. Since his appointment to the ARCHIVES Board, in 1952, he has participated actively and effectively in the affairs of the journal. His wise counsel and warm friendship have been a great boon to his associates in this enterprise. He will be missed.

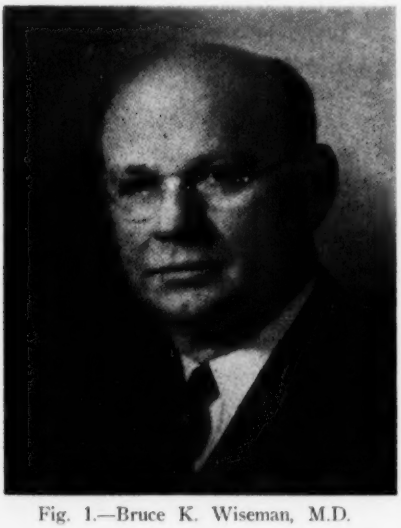

Fig. 1.—Bruce K. Wiseman, M.D.

Fig. 2.—C. Lockhard Conley, M.D.

Dr. C. Lockhard Conley, of The Johns Hopkins School of Medicine, will succeed Dr. Wiseman. Dr. Conley received his undergraduate work at Hopkins and was graduated from the medical school of Columbia University in 1940. He had had a fellowship in physiology in Maryland during 1936-1937. After being an intern and assistant at Presbyterian Hospital, New York, 1940-1942, he joined the faculty at Johns Hopkins and advanced through the ranks until he was appointed Professor of Medicine, in 1956. He has been in charge of the Hematology Clinic since 1947.

Among his many important posts are those of Consultant, U. S. Army; Veterans Administration, and U. S. Public Health Service; member of the hematology study section, National Institutes of Health 1952-1956; committee on blood coagulation, National Research Council, 1954-present; honorary associate professor of medicine, Guy's Hospital Medical School, London, 1957; secretary, antianemia preparations advisory board, "Pharmacopoeia, of the United States," 1954, Editorial Board, *Blood*.

He has membership in the Association of American Physicians, American Society for Clinical Investigation, American College of Physicians, Society for Experimental Biology and Medicine, American Medical Association, Interurban Clinical Club, and Alpha Omega Alpha.

Most of Dr. Conley's fifty-odd publications have been reports of investigations in the hematology field. His chief research interests have been in the mechanisms of blood clotting and in the disorders of the blood in disseminated lupus erythematosus. However, his original studies have been by no means confined to these subjects. His associates on the board welcome him with the confidence that he will make significant contributions to the ARCHIVES, as he has done in the other fields of his medical interests.

PAUL S. RHOADS, Chief Editor

Joint Responsibility

The large majority of pharmaceutical manufacturers are greatly concerned lest their good name be sullied by entrepreneurs who have entered the field without the traditional background. They are concerned that a sense of responsibility continue to permeate the drug industry. The relations of physicians and manufacturers of pharmaceuticals need review from time to time that we may jointly consider material problems. My purpose is to consider some of the relationships between physicians and the pharmaceutical industry.

The methods by which society protects itself in a democratic state in a capitalistic system depend on knowledge, on foresight, on wisdom, and, not least, on a sense of responsibility. These all must be diffused widely throughout the length and breadth of society to provide the guiding force for people in all walks of life. In the past, when science moved slowly and new innovations in therapy were based on inspirational ideas rather than on experiment, the sick patient might fare well or badly, not so much from the disease he had as from the therapeutic views of his physician. There were few specifics. When pharmacology advanced along the toilsome road of observation and experiment as chemistry grew up from alchemy and witchcraft, the specifics began to multiply. Now we have whole industries in search of ever more wonderful drugs. Modern medicine owes a tremendous debt to the pharmaceutical industry and could not exist without it. Nevertheless, there are certain dangers which need attention and honest comment.

Before a drug is released for distribution and sale it must satisfy certain requirements of purity. It must not exceed certain limits of acute toxicity. But regulations governing the purported efficacy of drugs are less stringent. Little has been done to guarantee safeguards against cumulative ill effects, intolerance to prolonged therapy, risks of sensitivity, or particular kinds of cell damage, as to the hematopoietic system.

The research contributions of individual members of the pharmaceutical industry have been enormous. Not only have they occurred as a result of grants in aid, but many drug manufacturing concerns have developed their own extensive laboratories. A distinguished investigator may be given completely free rein. Naturally, there is usually some pressure to work on problems of potential financial interest to the company. At the same time, much sound basic research is done and often with no ulterior motive. Where capable scientists are active, the quality of the work is excellent. Individual financial arrangements are attractive. The investigator is relieved of the responsibilities of teaching or practice. But even looked at in the best light, such research institutes are one-way streets. There is very little return to the academic arena. Such institutes are not self-reproducing, as the academic departments must be. They do not breed up their own replacements of scholarly investigators. The schools and universities must provide their own replacement of teachers and investigators, supply government agencies

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as well as industry. While the competition to get or to keep keen young men is great, we should remember the fate of those who kill the goose that lays the golden egg.

Physicians and apothecaries have a long and tangled story, highlighted by effective collaboration as well as violent antagonisms. The situation today needs attention and joint activity from physicians and leaders of the pharmaceutical industry, lest, in the freewheeling competition of the marketplace, policies and practices be determined casually and without exercise of responsibility. While leaders of industry may be pleased if altruism is a by-product, as businessmen in a competitive world they look upon drugs as a legitimate commodity, eligible for whatever exploitation and profit may be achieved within legal bounds. As with most complex situations, there are many aspects to this one. It will not be solved for the mutual advantage of all concerned unless it is faced directly. This must be done not only by government agencies but by physicians and leaders of the pharmaceutical industry, individually and collectively. I have no access to any secret documents with information not available to everyone, but these points need attention. For without study and forethought we may drift into a position of serious jeopardy at the very time when physicians and the pharmaceutical manufacturers are at the threshold of a time of even more effective and remarkable therapy.

The sciences of chemistry and pharmacology have advanced to the stage where knowledge of molecular structure may give a preview of probable pharmacologic function of chemical compounds before they are made. While Rauwolfia is an exception, we no longer get many useful leads from folk medicine. Once antibiotics were discovered there was a logical way to search for others. Steroid hormones are proliferating at a rapid rate along lines of more than educated guesswork. The mass production of virus vaccines is a latter-day wonder. Nirvana over the counter comes as the general public or any patient, well or ill, can eat pills for peace of mind, bestir his becalmed spirit with analeptics, and seek some mythical high-octane feeling with vitamins. Every man his own physician. Coached by what he hears or sees, he may demand of a physician the latest miracle cure announced in newspaper or over television before it has been described in scientific journals.

Now another side of the picture is seen in the ultimate fate of many a drug acclaimed as the latest and best cure. Promotion brings enthusiastic use. Then too often come gradual disappointment, delayed or bizarre reactions, disillusion, rejection and oblivion, or final acceptance suitable to the observed level of performance. No one has worked on the necrology of last year's sure cures, whose costly colored advertising brochures gather dust. What, in short, is the five-year survival rate of new drugs? Where are the cures of yesteryear? A study of abandoned drugs may seem a little foolish when so many new ones are arriving daily. But each failure is costly and wasteful—in time, money, hope, and perhaps in health.

What is the organizational structure in which physicians and a manufacturer of drugs, untrained in *medical* problems, may find themselves at odds? I am not concerned with the many fine pharmaceutical companies which exercise scrupulous caution in releasing new drugs. The problem is with companies whose sole concern is business. The stockholders' interest is in income. The richest earnings occur when a new variety or variation of a drug is marketed before competing drugs can be discovered, improvised, named, and released. This bonanza time may last

only a few months. Unless there are large earnings, the quick kill with the quick pill, the investment does not pay off. Commercial secrets must be kept dark, lest a competitor get the jump. Under this system it is impracticable to do tests extending over a long period of months or years to establish the range of usefulness and potential dangers from toxicity. Such tests usually have to be done in hospitals and often in medical schools, where secrecy in science cannot be tolerated. Thus, after extensive laboratory tests on toxicity and pharmacologic properties, but sometimes with a minimum of clinical trial, a drug may be marketed.

Legislation in a system where lobbies may exert strong pressures is not likely to lead opinion but follow it, and then only if sufficiently aroused. Man, collectively, has not shown notably progressive ideas in dealing with his own health and physical welfare. Thus, for a time at least, such monitoring of drug release as is done will be partly a matter of the conscience of the particular industrial concern. Here another conflict may arise. Many fine pharmaceutical manufacturers got their start from the foresight and enterprise of a pharmacist or a physician who founded the company. There was a sense of obligation to the public as well as pride in the good name of the company. The public was not solicited to buy. But two changes have occurred. Some large chemical manufacturers have entered the drug field or bought out established businesses. The professional founders of other companies have become remote with the passage of time and industrial expansion. The scientific and medical people who make and test drugs might find themselves at odds with the marketing, advertising, and sales divisions but without a strong voice in controlling events. The business man promotes the interest of the stockholder and aims to keep out of court.

What are the ways of promoting the sales of drugs, new and old? Four major avenues are (1) visits by detail men, (2) mailing of brochures and samples, (3) advertising in medical journals and "throw away" journals which have no subscription cost, and (4) the exhibits at medical meetings. None of these is bad in and of itself, but certain abuses and corruptions may occur. Some of the dangers and damages are self-evident.

Salesmen are interested in sales. If salvation can be gained too, so much the better. Naturally, special products are praised—those of the salesman's firm—often with a memorized monologue delivered with samples and the accompanying folders. The newer drugs get special treatment. The physician, if he is uncertain of what his fellow physicians may be doing, does not want to be left at the post in any new therapeutic race either. So, with the reassurances he gets, the new therapy is launched. The results are variable but not all according to the spiel.

A further form of beguilement is the employment of undergraduate medical students as apprentice detail men in the pay of some pharmaceutical concern to dispense samples and to instruct not only colleagues but also teachers in the latest therapeutic recommendations of his company. Those who would use such methods to bring their products to the attention of students, interns, residents, and physicians in hospitals have few scruples in sales promotion.

Advertising by mail must be effective, or it would not be so prevalent. The sample for the physician's personal use or for some handy patient works on the principle that a pill in the hand will be put into somebody's mouth. As a method of practice, it appeals to the lazy or hurried and harried physician. But it is the practice of expediency, not of mature thought. One never knows when the mail will bring a pillow and a pill for peace of mind. Samples may provide

an alarming toy for children playing at doctor or for those who are still curious. The drug sample is a poor substitute for thought in the practice of medicine.

The advertising by brochure may be the weekly, monthly, or quarterly house-organ variety, richly illustrated, sometimes with excellent scientific or quasiscientific articles. Often these are reproductions of classical or ultramodern paintings, stories, or poems, all by well-known artists and professional people. They have no bearing on medicine but attract attention. The extent to which this form of advertising has grown can be appreciated only by those who have observed the crowded mail rooms in hospitals or have taken the trouble to count and weigh the documents which daily descend upon us. Many are thrown away unopened. Thus a protective mechanism spares the more critical physician from what he considers a nuisance. If he studied the year's crop of five thousand mailings attentively, he could do little other reading. Children may enjoy the pretty pictures and, rarely, eat them.

Even the most respectable medical journals may have some questionable advertising. Advertising in some medical journals is screened in a cursory fashion by the editorial board or business management. With use of the Madison Avenue technique of innuendo, much of it seems to say more than it actually does. It stays within the law but hints strongly that our brand of "Libiduplift," "Three-blind-mycin" or "Poly-multi-every-vit" is the one and only and probably is the long-awaited panacea. Still, journal advertising is perhaps least objectionable and no one should be denied a chance to tell his story, if it is factual. It seems likely that much will never be in good taste.

Philosophers have scarcely examined the question of the teaching value of medical meetings. These range in scope from small county or town medical societies to such great conventions as the meeting of the American Medical Association or international congresses attended by thousands. Great medical organizations from the size of a state medical society and larger have many expenses in holding a medical meeting. They must pay for administrators, secretaries, mailings, programs, stenographic aid, rooms for the press, and a place for the meeting, including room for commercial and scientific exhibits. At the large meetings, there are reunions, dinners, banquets, organized activity for the wives, and less and less emphasis on strictly scientific portions of the program. In fact, to get to the lecture hall, it may be necessary to run a gauntlet through a maze of commercial exhibits. Special intermissions are scheduled in the scientific program for visiting the exhibits. Each exhibitor is expected to bring back evidence of attention in the form of the names of physicians who have registered at his booth. Society officers and those conducting meetings urge everyone to register at each exhibit and remind the audience that the society is beholden to the exhibitors for money to hold the meeting. The emphasis on strictly professional and scientific activities dwindles in comparison with the commercial aspects. Thus the medical meeting is expanding in its functions and risks becoming a partially tax-deductible holiday for the wife and family, an opportunity for a collection of bushels of samples and reams of brochures, as well as all the entertainment and sight-seeing trips.

Censorship has arisen in some medical societies which avoid scheduling papers by speakers who might be critical of the exhibitor's products. Some editors have refused to publish articles criticizing particular drugs and methods of therapy, lest advertising suffer. The employment of a veto power by societies which find

themselves so dependent upon support of this kind indicates a serious decline in medical responsibility, where the business management of a journal has usurped the physician's role as censor.

At certain meetings, various pharmaceutical houses maintain convenient rooms for the relaxation of their friends and clients. Cocktail parties are the order of the day. Lavish dinners may be held. These seem to be free. Instead, they are supported by increasing the cost our patients pay for drugs.

There have been a few tragedies and other near misses. Once sulfonamides were dispensed in a variety of antifreeze because it was a good solvent. Many persons were killed. But the pharmaceutical industry now is doing a splendid job of keeping up standards of purity. It is in the widespread use of new compounds which may have serious risk of cumulative toxicity, special sensitizing proclivities, or other effects where the problem is serious. Responsible persons in medicine, government, and industry must face these issues together, honestly and courageously, lest there be truth in the statement that the public is now screening new compounds so that pharmacologists in their laboratories know their toxicity before they study them in guinea pigs.

In "Ecclesiasticus," a book which was relegated to the Apocrypha rather than put in the Bible as a result of a curious ancient ecclesiastical popularity contest, we find these words, "For a man's soul is sometimes want to tell him more than the seven watchmen that sit above in an high tower." Is our collective conscience too dependent on others at a time when the very word controversial has become anathema? Physicians and responsible members of the pharmaceutical industry have an obligation to examine controversial matters in order that, collaborating effectively, apothecaries and physicians change their ancient traditions of antagonism. Only thus will the best interest of society be served.

WILLIAM B. BEAN, M.D.

Functional Types of Acute Renal Failure and Their Early Diagnosis

WILLIAM H. WAUGH, M.D., Augusta, Ga.

Since it is important diagnostically and therapeutically to recognize the factors responsible for a given case of acute renal failure, a classification of the various functional types of acute uremia should prove of clinical usefulness. The designation extrarenal azotemia does not appear to serve a very useful purpose in this regard, since such a term does not appropriately indicate the insufficient renal function which is usually present in the so-called extrarenal azotemias. Even the term extrarenal uremia is ambiguous and conducive of confusion for the obstructive or "postrenal" uremias have not been classified as extrarenal uremias,[1,2] as they should be semantically. The purpose of this paper is to suggest a clinically useful functional classification for the acute uremias, to review briefly the chief functional types of acute renal failure while relating pathophysiologic processes in the kidney to a few important urinary signs, and to point out practical aids with which the early differentiation of the acute uremias can usually be accomplished.

Concept of Extrinsic and Intrinsic Renal Failure

Since the acute loss of normal renal function or the acute inability of the kidney to maintain a normal internal environment is due to either extrarenal or intrarenal factors, the acute renal failures may be divided into two broad functional types, extrinsic failure and intrinsic failure. Extrinsic renal failure may be defined as renal insufficiency due to extrarenal factors or disturbances which continually act on the kidney, removal of which is followed by prompt and virtually complete return of kidney function to normal. Extrinsic renal failure may be caused by such factors as dehydration, salt depletion, general circulatory insufficiency, reflex renal ischemia, and obstruction of the urinary tract below the renal pelvis. Oliguria is common to all disorders classified as instances of acute extrinsic renal failure, and this oliguria may be promptly reversed by adequate therapy directed extrarenally.

On the other hand, the loss of normal renal function may be due to factors inherent in the kidney. Acute glomerulonephritis, acute pyelonephritis, renal cortical necrosis, and acute tubular necrosis ("lower nephron nephrosis"), either nephrotoxic or ischemic in origin, are all instances of acute intrinsic renal failure. In such intrarenal disorders, renal function is not promptly and completely restored to normal by any presently known means, although the renal failure may frequently be reversible over a period of days or more if the initial insulting factors are removed.

Functional Types of Acute Extrinsic Renal Failure

In the acute extrinsic renal failures, either the glomerular filtration of both water and solute is considerably reduced in the whole mass of nephrons and the filtrate passes down tubules which retain, at least initially, relatively normal reabsorptive functions[2] or the glomerular filtrate is formed at a normal or near-normal rate in virtually all nephrons. There is, neverthe-

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From the Departments of Medicine and Physiology, Medical College of Georgia.

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less, an excessive renal retention of water and solute due to tubular reabsorption mediated through the action of humoral substances, such as sodium-retaining or antidiuretic agents.[3,4] In both of the above extrinsic types of acute renal failure, the urine is characteristically low in volume, low in sodium concentration, but high in specific gravity because filtered solutes other than sodium salts (chiefly urea) have been concentrated by tubular reabsorption of water. Thus, the specific gravity of this acutely oliguric urine is usually above 1.018 and its urea concentration above 2.0 gm. %, even though its sodium and chloride concentration is usually less than 20 mEq. per liter.[3,4] If an episode of extrinsic renal failure is sufficiently severe or prolonged, tubular damage or a functional amputation of whole nephrons may intervene with the development of a renal syndrome of intrinsic renal failure.

Functional Types of Acute Intrinsic Renal Failure

In acute intrinsic renal failure, oliguria is also commonly found, but the specific gravity, urea and sodium concentration of this oliguric urine is dependent upon the functional type of failure present. In primary diffuse glomerular disease, e. g., in acute glomerulonephritis, a generalized reduction in glomerular filtration sufficient to cause acute oliguria usually occurs before there is much tubular damage. Similar to the oligurias of acute extrinsic renal failure, the oliguric urine of acute diffuse glomerulonephritis is characterized, at least in the first few days, by a specific gravity above 1.018 and a low sodium concentration.[5] On the other hand, the oliguric urine formed during acute intrinsic tubular disease has different features. In acute tubular necrosis the urine has from the first a specific gravity which tends to approach that of a filtrate of plasma (about 1.010)[6] and usually has a sodium concentration of over 30 mEq. per liter even in the face of body needs for sodium conservation.[6,7] In bilateral cortical necrosis hyposthenic oliguria is similarly an early sign.[8] The fact that the renal damage of both acute tubular necrosis[9] and renal cortical necrosis[8] is patchy in nephron distribution and/or largely concerns proximal tubular segments has functional consequences. An increased load of blood solute is presented to a certain number of relatively intact nephrons or distal tubules with resultant osmotic "diuresis." It has been shown that such an osmotic effect is partly and perhaps largely responsible for the early low specific gravity and urea concentration of the urine in acute tubular necrosis.[10] Distal tubular injury also contributes to the early hyposthenuria of acute tubular necrosis.[10] Thus, even the early development of hyposthenuria without any oliguric phase after an ischemic or nephrotoxic insult, which occurs not infrequently,[11,12] should make one wary of acute tubular necrosis or patchy intrinsic renal failure.

A few authors, e. g., Taylor,[12] have exceptionally reported initial specific gravities of the urine slightly higher than 1.018 during the early phase of acute tubular necrosis, and one case has been reported with a much higher initial urinary specific gravity.[13] Severe dehydration was, however, obvious clinically during the acute oliguria with urine of very high specific gravity (1.027) observed in this case by Partenheimer, Boyer, and Citron.[13] These authors were apparently dealing with the early oliguria of a mixed syndrome of acute extrinsic and intrinsic renal failure. The recent work of Bull and his collaborators[7,10] strongly supports the viewpoint that if urine is formed with a nonprotein specific gravity above 1.018 even during the early oliguric phase of acute tubular necrosis the concentrated urine is due to associated extrinsic factors, such as dehydration or reflex effects.

Simplified Method for Early Differentiation of Acute Renal Failures

It has been pointed out that the dietary intake of total excretable solute and water may be reduced in near fasting patients in the proper proportions to cause a simple

physiologic oliguria with urine of specific gravity less than 1.018.[6] This simple oliguria which is neither associated with dehydration nor complicated by renal insufficiency is associated with a low urinary specific gravity chiefly because the urine is deficient in both urea and sodium salts. Since the urinary sodium concentration is less than 20 mEq. per liter,[6] this physiologic oliguria can thus frequently be differentiated from the acute oligurias of tubular necrosis or patchy intrinsic renal failure. It can be definitely distinguished from patchy intrinsic renal failure for in this physiologic oliguria the urine to plasma ratio of urea concentration greatly exceeds 20. In patchy intrinsic renal failure this urea ratio is less than 20 even in the occasional case, as following severe trauma or surgery, in which the urinary sodium level is less than 30 mEq/L.[11,12]

Thus, in this day of elaborate diagnostic procedures, there remains a simple method which is very helpful in the early diagnosis of acute renal failure and in the early differential diagnosis of the type of acute renal failure which is present, provided, however, the failure develops in previously normal kidneys. This method involves the measurement and interpretation of the volume, the specific gravity, and the sodium (or chloride) concentration of the urine and is summarized in the Table.

Typical Urinary Signs for the Early Diagnosis of Acute Renal Failure

	Early Urinary Features		
Type of Failure	Vol.	Specific Gravity *	Sodium Concentration, mEq/L.
Extrinsic renal failure (e. g., acute circulatory insufficiency)	Oliguric	Above 1.018	20 or less
Intrinsic renal failure, diffuse glomerular (e. g., acute glomerulonephritis)	Oliguric	Above 1.018	20 or less
Intrinsic renal failure, tubular or patchy (e. g., acute tubular necrosis)	Oliguric	Below 1.018	30 or more

* This properly refers to the nonprotein specific gravity. Since the urinary specific gravity is raised about 0.003 for each gm. % of protein present, the nonprotein specific gravity should be estimated in differentiating the acute oligurias if massive or "4+" proteinuria (above 0.5 gm. %) is present.

For the early differentiation of the acute azotemic syndromes, a practical or bedside method for the measurement of urinary sodium content would be of help. Even the determination of sodium by the rapid technique of flame photometry is not generally available outside most of the larger hospitals. On the other hand, analysis of the chloride content of the urine is a very useful substitute for the direct determination of sodium in the differentiation of the acute renal failures. Changes in urinary chloride concentration usually parallel the changes in urinary sodium concentration, and in the acute oligurias the difference in urinary sodium and chloride concentration is usually less than twofold.[3,7] A simplification of Scriber's modification [14] of the standard Schales method for measuring chloride is admirably useful for the functional differentiation and management of the acute azotemias at the bedside. In this test,* with the same dropper or with droppers of the same caliber, 1 drop of indicator is added to 10 drops of urine, and then 2.0% mercuric nitrate reagent is added dropwise until a permanent purple color is formed. Each drop or volume of mercuric nitrate added to produce the colored end-point corresponds to 10 mEq. of chloride per liter.

Comment

Joekes, Mowbray, and Dormandy [6] have emphasized that examination of the urine, preferably of each individual specimen, is most important in the early diagnosis and, therefore, correct management, of acute tubular necrosis. Early examination of the

* Indicator: Dissolve about 200 mg. diphenylcarbazone (Eastman Kodak) in 100 ml. 95% ethanol and store in light-tight bottle.

2.0% Mercuric Nitrate Reagent: Add 10.0 gm. mercuric nitrate [$Hg(NO_3)_2 \cdot H_2O$] to about 100 ml. distilled water; then add 20 ml. concentrated nitric acid, and dissolve; dilute to 500 ml. with distilled water.

urine also deserves emphasis in order to establish a general diagnosis of acute renal failure and in order to distinguish between the various functional kinds of acute renal failure. This is particularly true today because recent work seems to indicate that the acute renal failure of diffuse glomerulonephritis can be reduced in magnitude and the prognosis modified by very early therapy (e. g., fasting) directed at the initial mechanism responsible for the acute glomerulonephritis.[15] Early urinary examination for purposes of differential diagnosis is also very helpful in deciding in a given uremic person whether dialysis should be instituted relatively early, either by means of an artificial kidney [16] or by the simple technique of peritoneal dialysis [17,18] for two hours, repeated as needed.

Summary

The acute azotemic syndromes have been reviewed from a dynamic viewpoint and the thesis developed that acute renal failure may be profitably classified into functional types of extrinsic and intrinsic renal failure. The early functional differentiation of the acute renal failures has been emphasized, and practical means of urinalysis have been delineated which are very helpful in accomplishing this early differentiation.

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Renal Tubular Changes in Acute Glomerulonephritis

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Although tubular pathological changes and functional derangements have been noted to occur in patients with acute glomerulonephritis, these have been overshadowed by the severer glomerular abnormalities. In the present study the aim was twofold: to evaluate progressive changes in tubular pathology and to attempt to correlate them with alterations in tubular function.

Methods

Patients with acute glomerulonephritis were biopsied as soon as the diagnosis was suspected. Biopsies were done as previously reported,[1] with the patients lying prone and by means of the Turkel needle. Within a few days of the biopsy renal-function tests were done. These included the measurement of glomerular filtration rate by inulin clearance, effective renal plasma flow by sodium *p*-aminohippurate (PAH) clearance, and tubular function by Tm_{PAH}.[2-4] Thereafter patients were followed clinically and by frequent urinalyses. At approximately one month after the first studies, repeat biopsies and function tests were performed. Whenever feasible these were again repeated at later intervals, ranging from 233 days to 3 years after the onset of the illness.

Twenty-three patients with acute glomerulonephritis were studied. Patients having acute membranous glomerulonephritis were omitted, and only those with acute proliferative or hemorrhagic glomerulonephritis were included. Of the latter, 14 patients had both renal biopsy and function tests performed, and in 8 patients these studies were repeated.

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From the Departments of Medicine and Pathology of The George Washington University School of Medicine, Veterans Administration Hospital, and The George Washington University Medical Service of the District of Columbia General Hospital.

Results

The pathological changes observed in the tubules were divided into three types for ease of comparison. These were vacuolation of tubular cytoplasm, degeneration of tubular epithelium, and proximal tubular dilatation. Because coarse vacuolation of tubular epithelial cells is seen in about 80% of all biopsy specimens regardless of the presence or type of renal disease or the state of tubular function, little significance was attached to its presence. Fine vacuolation involving the entire cell was considered to be definitely abnormal, as was the finding of large vacuoles replacing most of the cytoplasm. Degeneration was judged to be present when varying degrees of epithelial cellular necrobiosis or necrosis were found, from pyknosis of nuclei and loss of cellular detail up to and including complete sloughing of cells into the tubular lumina. The third lesion consisted of dilatation of the lumina of the proximal convoluted tubules due to the replacement of the normal columnar epithelium by rows of flattened cells. Most of the tubules thus involved showed no actual increase in diameter. Their lining epithelium, though flat, contained large, elongated, hyperchromatic nuclei, and there was no evidence of atrophic changes. A smaller number of proximal convoluted tubules were actually dilated, however, and their flattened epithelium appeared to be atrophic. These lesions usually occurred together and were therefore included together under the term dilatation.

Figure 1*A* shows normal proximal and distal convoluted tubules in cross section. Note the occasional coarse vacuoles in the epithelium of the proximal convoluted tubules. Figure 1*B* demonstrates vacuolation in a biopsy specimen taken eight days after

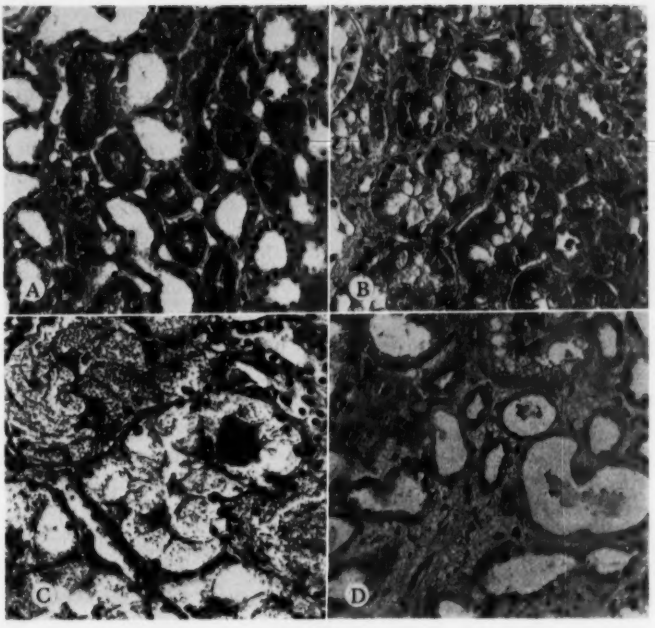

Fig. 1.—Renal needle biopsies from (*A*) normal; (*B*), (*C*), and (*D*), acute glomerulonephritis (see text for descriptions).

the onset of renal symptoms. The epithelium of the proximal convoluted tubules contains numerous coarse and fine vacuoles throughout the cytoplasm. Figure 1*C* is an example of degeneration from a biopsy specimen taken five days after the onset of symptoms. The epithelium of the proximal convoluted tubules shows cytoplasm which is markedly swollen, coarsely granular, and finely vacuolated. The cell nuclei are small, pyknotic, and frequently completely absent. Figure 1*D* exemplifies dilatation. Many of the proximal convoluted tubules show dilated lumina and are lined by a flattened layer of epithelium having irregular hyperchromatic nuclei. This photomicrograph is from a biopsy specimen obtained 28 days after the onset of renal symptoms.

TABLE 1.—*Occurrence of Renal Tubular Changes in Relation to Time of Biopsy*

Time, Days	Vacuolation, %	Degeneration, %	Dilatation, %	Total
0-14	36	27	27	11
15-30	63	25	75	8
31-60	18	18	64	11
>60	11	0	44	9

Thirty-nine successful biopsies were done in twenty-three patients. Initial biopsies were performed from 5 to 27 days from the onset of symptoms of renal disease. Those done within the first two weeks showed abnormal vacuolation in 36%, degeneration in 27%, and proximal tubular dilatation in 27% (Table 1). It can be seen that abnormal vacuolation and degenerative changes were most frequent within the first month and later decreased rapidly with recovery. Dilatation was most marked at 15 to 30 days and disappeared more slowly. In six of eight patients who showed dilatation initially, there was complete disappearance of the lesion on subsequent biopsy.

Renal-function tests were performed 20 times in 14 patients (Table 2). These data show the expected improvement in inulin and PAH clearances as the patients recovered. The average value for Tm_{PAH} was abnormal only in the first two weeks, but it can be seen from the ranges obtained

TABLE 2.—*Relation of Renal Function to Time from Onset of Renal Disease* *

Time, Days	Patients, No.	C_{Inulin}, Ml/Min.	C_{PAH}, Ml/Min.	Tm_{PAH}, Mg/Min.	F. F.
0-14	5	48	227	53	0.21
		(15-74)	(86-498)	(6-96)	(0.07-0.35)
15-30	6	81	524	82	0.15
		(30-138)	(174-1525)	(8-132)	(0.10-0.21)
31-60	7	92	628	85	0.15
		(58-137)	(366-922)	(40-134)	(0.08-0.33)
>60	2	101	470	78	0.21
		(95-107)	(432-508)	(73-84)	(0.16-0.30)

* Numbers in parentheses represent the range of values obtained.

that the Tm_{PAH} in some patients was normal from the start, whereas in others it remained abnormal for as long as two months. The two patients with follow-up renal function studies at 422 days and at 3 years both had normal values for Tm_{PAH} and clinical evidence of recovery.

When paired functions and biopsies were repeated and when these patients were compared only with themselves, six out of eight showed a rise in Tm_{PAH}. Histological changes accompanying this rise were variable; three showed improvement; two remained unchanged, and one showed proximal tubular dilatation which had not been present on the first biopsy. One patient whose Tm_{PAH} was markedly depressed initially and whose biopsy specimen revealed tubular vacuolation and dilatation progressed clinically to chronic glomulonephritis and death. His renal functions showed no improvement at 133 days; promixal tubular dilatation persisted, but vacuolation disappeared. These changes were confirmed at autopsy. The second patient whose Tm_{PAH} did not rise showed complete clearing of his tubular pathology at 60 days, and he appears to have recovered.

Comment

With the advent of the needle biopsy as a diagnostic tool it has been possible to follow the morphological changes during the course of glomerulonephritis.[5] Howe, in 1955,[6] described degeneration and sloughing of tubular epithelium early in the course of acute glomerulonephritis, followed by evidences of regeneration on later biopsy. Pollak et al.[7] found similar tubular degeneration in serial biopsy specimens of a patient with acute glomerulonephritis, with some moderate degenerative changes persisting 11 months after the first biopsy. A recent publication by Hutt et al.[8] stressed the finding of tubular degeneration and dilatation early in the course of acute glomerulonephritis. In the cases observed by us, frank degeneration of the tubular epithelium was the least common finding, being present in only seven patients biopsied between 5 and 40 days from the onset of their renal disease. It was never found on repeat biopsy, when the acute phase of the disease appeared clinically to be subsiding. Sixteen patients showed no evidence of degeneration, regardless of the time of biopsy.

Fine vacuolation tended, in general, to disappear with recovery. Most frequently it seemed to precede or accompany degeneration, but this was not consistent, since it was sometimes present on the second biopsy yet absent in the first. The identity of the vacuoles was not established. It is noteworthy that none of the patients reported here had hypokalemia, so that this cannot account for the presence of the vacuoles.

The lesion which we are designating as dilatation was the slowest to disappear. The large hyperchromatic nuclei seen in the flat epithelial cells of most of the dilated tubules suggested that these were young, actively growing cells. This change was therefore interpreted as being evidence of attempted repair after tubular necrosis in the stage of degeneration. The persistence of dilatation

after vacuolation and degeneration had subsided further suggests that this is a reparative process. The fact that initial biopsies in 10 patients showed dilatation of proximal tubules without evidence of degeneration possibly indicates that the degenerative changes may occur promptly in the course of the disease and that they may have come and gone by as early as six days after the onset of renal symptoms. The presence of fewer actually dilated and atrophic proximal convoluted tubules suggests that there may be some element of "internal hydronephrosis" owing to plugging of distal tubules by protein casts, as has recently been described.[9]

Serial measurements of renal function in patients with glomerulonephritis by numerous investigators [10-13] have shown a reduction in Tm_{PAH} or $Tm_{Iodopyracet}$ ($Tm_{Diodrast}$) in the majority of patients during the acute phase, accompanying the expected reduction in glomerular filtration rate, with return toward normal on healing. Some authors, notably Brod [14] and Van Slyke,[15] have stressed the functional importance of tubular failure in acute glomerulonephritis. In a previous paper, Parrish, Rubenstein, and Howe [16] showed that a fairly good correlation existed between glomerular filtration rate and estimated glomerular pathology in patients with glomerulonephritis. In the present series of patients a good correlation can be demonstrated between Tm_{PAH} and glomerular filtration rate (Fig. 2), showing that the depression in tubular excretion of PAH approximately parallels the depression in glomerular filtration. This would imply that the tubular functional defect might be secondary to the primary glomerular disease. It is likely that this results from the decrease in blood flow through the glomerulus, produced by the increased cellularity and decreased vascularity which occurs.

When an attempt was made to compare the functional state of the tubule, as measured by Tm_{PAH}, with the estimated degree

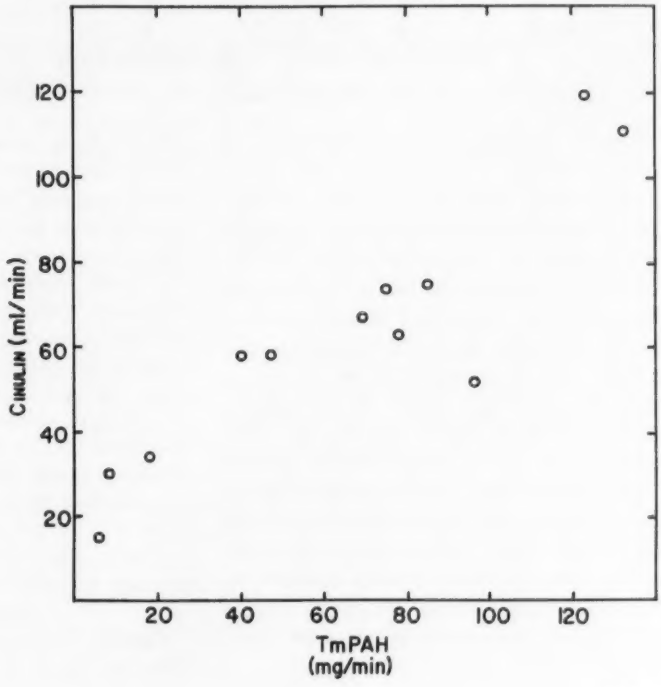

Fig. 2.—Relation between filtration rate (C_{Inulin}) and tubular function (Tm_{PAH}) in acute glomerulonephritis.

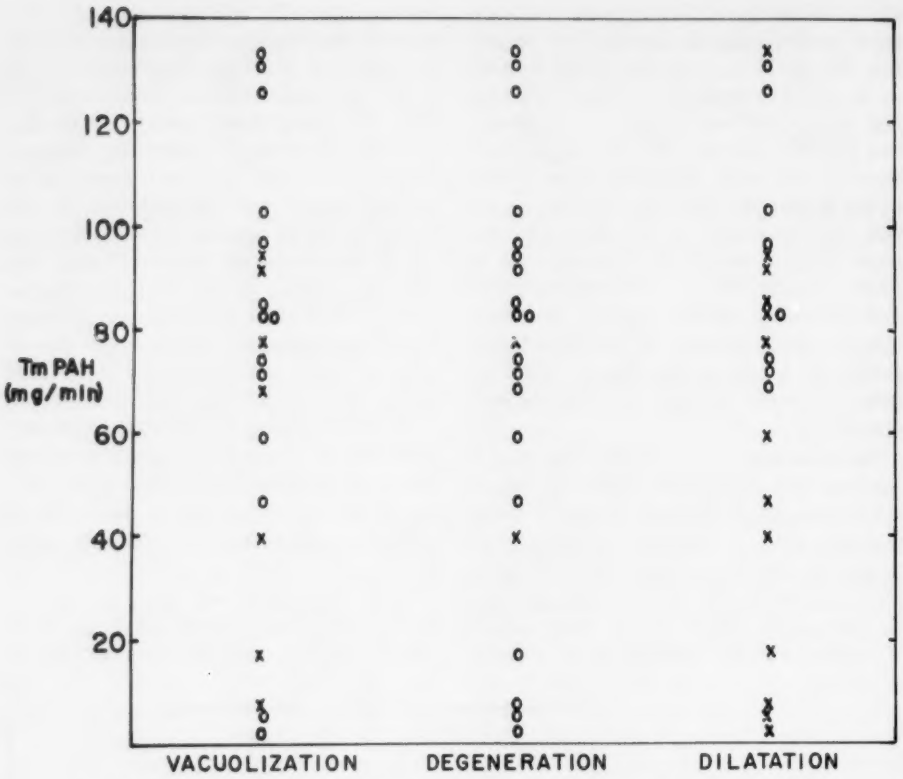

Fig. 3.—Relation between tubular functions and pathology in acute glomerulonephritis.

of tubular pathology no consistent relationship could be demonstrated. The initial Tm_{PAH} value could not be correlated with the presence or absence of tubular epithelial degeneration or vacuolation (Fig. 3). Although all patients with Tm_{PAH} values below the lower limits of normal showed proximal tubular dilatation, this abnormality was also found in 6 of 14 patients with normal or supernormal Tm_{PAH} levels. If dilatation is indeed attempted tubular regeneration, this would imply that a rising Tm_{PAH}, though signifying functional improvement, does not necessarily parallel morphological evidences of tubular repair. Unfortunately, those patients with the most striking changes in tubular epithelium were also anuric, and so no function tests could be done for comparison.

The lack of definite correlation between Tm_{PAH} levels and the degree of tubular pathology suggests that possibly the changes that are seen are not functionally significant. This seems unlikely especially when degenerative tubular changes are present. It appears, rather, that the pathological abnormalities seen have little influence on the function of tubular transport of PAH. From the cases presented it would seem premature to conclude that all patients with subnormal Tm_{PAH} levels will have tubular dilatation, as our data show. It seems more probable that the level of Tm_{PAH}, especially when it is in the normal range or above, is of little value in predicting the pathology that will be found on biopsy.

Summary

Tubular changes were studied in 23 patients with acute glomerulonephritis. Early

pathological lesions consisted of epithelial vacuolation, degeneration, and proximal tubular dilatation. Later the vacuolar and degenerative changes subsided, whereas dilatation continued. Tubular function, as measured by the maximal tubular transport of PAH, showed improvement as the patient recovered but held no consistent relationship to the pathology.

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Asian Influenza—Clinical Picture

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Of the great plagues that in past centuries regularly decimated the world population, only influenza remains. The recent pandemic of Asian influenza made very manifest the limits of our progress in the conquest of this scourge. Currently we know and can study the causative agent, have a good but far from perfect vaccine, and can treat most complications successfully. Incomplete is our knowledge concerning the clinical symptoms associated with influenzal infection, the variations in number and intensity of these symptoms, and their complications and sequelae. For these reasons it is appropriate to present and to record the complete clinical picture, observed in the New Orleans area during August, September, and October, 1957, in 76 patients who suffered from influenza, established by specific diagnostic tests to be due to influenza Type A, Asian strain.

Background

This study, one of many planned and initiated by the threat of an impending invasion of the United States by Asian influenza, was completed at the Charity Hospital of Louisiana, in New Orleans. It represents a portion of a large-scale investigation of Asian influenza which was effected by the Department of Medicine of Tulane University School of Medicine. The purpose which these studies served was one of medical intelligence. They were specifically designed to obtain information upon which could be based a sound program of preparedness. This was possible since, with the exception of scattered local epidemics caused by travelers, Louisiana was the first state to experience a large-scale epidemic of influenza. The first scattered cases appeared in late June, increased in number in July, reached epidemic proportions in mid- and late August, and had become infrequent by late September, 1957. The city of New Orleans, from which Charity Hospital draws most of its patient population, witnessed the epidemic largely run its course between mid-August and mid-September, 1957.

Materials and Methods

From the beginning it was planned that the investigation be limited to "proven" cases studied intensively in the hospital. Since confirmatory laboratory tests were not completed until after the patient had been discharged to home care, not all patients studied are included in this report. Further attrition was due to incomplete follow-up and the limitation of personnel and equipment. Approximately one-third of the patients were hospitalized for either of the following reasons:

(*a*) As patients of the outpatient department of Charity Hospital who presented a classical clinical picture of influenza, they were admitted to the wards for study purposes.

(*b*) Their position as members of the professional staff of a hospital distant from their homes precluded adequate home care.

The remainder of the patients were hospitalized in one of several medical facilities because of the severity of their symptoms. For these reasons this was a preselected group.

The selection of the patients was further qualified by limitation to those patients in whom the diagnosis of Asian influenza comprised virus recovery and/or a fourfold or greater rise in hemagglutination inhibition antibody (HIA) titer.

In addition to routine clinical and laboratory studies, whenever practical patients were subjected to determinations of renal and hepatic function, measurements of fluid and electrolyte metabolism, serial electrocardiographic and spatial vector-

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From the Department of Medicine, of the Tulane University School of Medicine, Charity Hospital of Louisiana, and the U. S. P. H. S. Hospital.

TABLE 1.—*Sex, Color, and Age Incidence of Patients with Pneumonia in Seventy-Six Patients with Asian Influenza*

	Influenza	Pneumonia	Total
Males	34	8	42
White	15	5	20
Negro	19	3	22
Females	27	7	34
White	5	2	7
Negro	22	5	27
Age, Yr.			
0-9	1	0	1
10-19	14	0	14
20-29	27	4	31
30-39	15	7	22
40-49	2	1	3
50-59	--	--	--
60-	2	3	5

cardiographic examinations, rheoplethysmographic determinations of the state of digital blood flow, estimation of adrenal cortical function, bronchoscopic and cytologic examination, and bronchial biopsy. For the various reasons mentioned, all of these and many other essentially routine examinations were not performed on all patients.

This report is concerned with 76 patients in whom the clinical diagnosis of Type A influenza, Asian strain, was confirmed by the specific diagnostic measures described previously. Table 1 summarizes the age, sex, and racial distribution of the patients, a distribution expected from the nature of the study and the patient population of Charity Hospital.

Results

Contact.—Thirty of the patients (39%) gave a history of contact with influenza within the several days preceding onset of their illness. A large portion of this group was composed of professional or semiprofessional personnel and of patients seen late in the study, when the local epidemic was at its peak.

Prodrome.—Of the 76 patients, there were 12 who gave a history of respiratory enzal syndrome. Almost invariably this was mild upper respiratory tract infection of infection preceding the onset of the influless than one week's duration. One patient, who was treated for pneumonia two weeks prior to admission, stated he had rapidly become asymptomatic until four or five days prior to hospitalization, when his respiratory symptoms recurred and progressed in severity. The upper respiratory tract infections preceded the influenzal infection one-fourth as frequently in patients with uncomplicated influenza as in the patients who suffered from influenza complicated by pneumonia. In the former group the course of the influenzal infection did not appear altered. However, the greater frequency of preceding respiratory infections in the patients with influenza complicated by pneumonia may be due to several possibilities. For example, potentiation of bacterial virulence by influenza has been demonstrated. Perhaps the converse holds true and results in greater invasion of the tracheobronchial tree by the viral infection and impairment of local and constitutional defense mechanisms. Possibly, the presence of an established bacterial flora facilitates bacterial invasion after influenza has damaged the respiratory mucosa.

Onset.—Of the 76 patients, 66 described the onset of influenzal symptoms as acute. Of the remaining 10 patients, 8 noted for several days the steady increase in the severity of a preceding respiratory infection and 2 noted the gradual onset of typical influenzal symptoms over a period of 18 to 24 hours. The first symptoms were headache, fever, chilly sensations, or myalgia, singly or together. Although invariably the symptoms increased in intensity with the passage of time, the patients were usually very ill very early in the course of their illness.

Symptoms.—Table 2 lists the frequency of various symptoms encountered. Fever,

TABLE 2.—*Incidence of Symptoms Elicited from Seventy-Six Patients with Asian Influenza*

	No.
Fever	66
Myalgia	50
Headache	49
Chills	47
Cough	37
Conjunctival irritation	23
Sore throat	19
Chest pain	19
Dyspnea	13
Nausea and/or vomiting	10
Hemoptysis	8
Abdominal pain	2
Epistaxis	1

chills or chilly sensations, myalgia, and headache constituted the usual symptom complex in patients with uncomplicated influenza, although cough and conjunctival discomfort or tearing each occurred in about one-third of such patients. A slightly smaller group complained of a scratchy sore throat, and about one in six complained of retrosternal aching or a tight feeling in the chest. Conversely, 7 of the 15 patients with pneumonia experienced chest pains, although in only one instance was this typically pleuritic in type. Of the 15 patients with influenza complicated by pneumonia, cough occurred in all 14 who could complain (one patient was comatose on admission). In contradistinction to the irritating cough productive of small amounts of mucoid material encountered in influenza, the pneumonia group experienced severe protracted coughing productive of variable amounts of mucopurulent material. Blood-streaked sputum was noted by 3 of the 61 patients with uncomplicated influenza and by 5 of the 15 patients with influenza complicated by pneumonia.

Dyspnea was mentioned by only one patient with uncomplicated influenza. However, when simple influenzal infection occurred in conjunction with various other medical conditions, dyspnea was a feature of the symptom complex, i. e., two patients with mitral stenosis, two patients with bronchial asthma, one patient with acute rheumatic pericarditis, and a child with typical acute laryngotracheal bronchitis. Both patients with rheumatic mitral stenosis experienced paroxysmal nocturnal dyspnea, with the production of frothy pink sputum. Among the 15 patients whose influenzal infection was complicated by pneumonia, dyspnea occurred in 6. Abdominal pain, epistaxis, nausea, and vomiting were rarely encountered.

Analysis of the above data indicated that although the typical clinical picture of influenza was present in most patients, dyspnea rarely occurred with uncomplicated influenza. Its presence usually signified complications involving the cardiopulmonary system. Hemoptysis and chest pain occurred more frequently in patients with complicating pneumonia than in patients with simple influenza, but they were not specifically indicative of pneumonia.

TABLE 3.—*Incidence of Physical Findings in Seventy-Six Patients with Asian Influenza*

	No.
Nasopharyngeal injection	51
Conjunctival injection	30
Alteration of breath sounds	13
Rhonchi and/or wheezing	10
Cervical	9
Crepitant rales	9
Bronchial breathing	7
Dullness	4
Facial flushing	4
Cyanosis	2
Venous distention	2

Physical Findings.—Table 3 summarizes the physical findings. With the exception of nasopharyngeal injection and conjunctival suffusion, patients with uncomplicated influenza presented few abnormal physical findings. Rhonchi and wheezing were noted in uncomplicated influenza (four patients), in influenza complicated by pneumonia (two patients), and as in the four patients who suffered from preexisting bronchial asthma.

The following abnormal physical findings were encountered only among the 15 patients with a complicating pneumonia or the 3 patients with congestive heart failure: crepitant rales, bronchial breathing, dullness to percussion, venous distention, cyanosis, or pericardial or pleural friction rub. Of interest is the alteration in breath sounds, best described as exaggerated vesicular breathing, which was encountered in at least eight of the patients with simple influenzal infection. It is apparent that in this series of patients the presence of abnormal physical findings on examination of the chest was indicative of cardiopulmonary complications, although their absence did not preclude the presence of such complications. The altered breath sounds, noted in patients with uncomplicated influenza, were of interest to the examining physicians but were not a source of diagnostic error.

One patient with severe meningoencephalomyelitis presented in a semicomatose condition with hyper- and hyporeflexia, bilateral Babinski responses, and definite sensory impairment. All of these findings eventually disappeared.

Specific Diagnostic Tests.—Throat washings were obtained from all patients and inoculated in embryonated eggs, as were nine bronchial biopsy specimens. Thirty of the former and two of the latter yielded Asian strain influenza virus. Paired sera, obtained over a 14-day period, revealed in 67 instances a fourfold or greater rise in hemagglutination-inhibition antibody titer, specific for Asian strain influenza A.

Roentgenology: X-ray examination of the chest was made in all patients. In 13 instances, a pneumonic process was apparent in the right (5) or left (3) or both (5) basal lung fields. There were two patients with involvement of the right mid- and upper lung fields exclusively. All infiltrates cleared promptly with appropriate antibiotic therapy. Two of the patients with heart failure showed appropriate congestive changes in the initial roentgenographic examination of the lungs.

Hematology: The erythrocyte sedimentation rate was elevated in all five of the patients with complicating pneumonia in whom such a measurement was made. Conversely, of 38 patients with single influenzal infection who were similarly observed, 10 had a normal value. The total white blood cell count was greater than 10,000 cells per cubic millimeter in slightly more than one-half (8 of the 15) of the patients with pneumonia complicating the influenzal infection. Similar laboratory determinations, made in 61 patients with influenza, yielded counts below 10,000 cells in 52 instances. There were four patients with values exceeding this figure, who suffered from bacterial complications other than pneumonia (streptococcal tonsillitis, bronchitis, sinusitus, and conjunctivitis). Five patients with simple influenzal infection exhibited total white blood cell counts of greater than 10,000 but less than 15,000 cells per cubic millimeter. Of 50 patients with uncomplicated influenza, 27 had a normal differential white blood cell count and 13 had a lymphocytosis. Polymorphonuclear leukocytosis occurred in four patients with influenza complicated by nonpneumonic bacterial infection and in six patients with simple influenzal infection.

Of the 15 patients with influenza complicated by pneumonia, 9 had a polymorphonuclear leukocytosis; 4 had a normal white cell count, and 2 had a slight lymphocytosis.

The above data indicate that 12 of the 15 patients with influenza complicated by pneumonia had an elevation of either the total white blood cell count or the proportion of polymorphonuclear leukocytes. Only 5 of 57 cases of simple influenza uncomplicated by bacterial infection of any sort presented a total white blood cell count exceeding 10,000 cells per cubic millimeter (none of these was greater than 15,000). Of these 57 patients 4 exhibited a normal leukocyte count, with mild polymorphonuclear cytosis in differential counting. Thus, in this series, an elevation of the total white blood cell count beyond 15,000 cells per cubic millimeter or a polymorphonuclear leukocytosis almost always indicated a bacterial complication.

During the first 10 days of hospitalization, the patient with influenzal encephalomyelitis exhibited a fall in the hematocrit from 39 to 25. Simultaneously, he was noted to have become slightly icteric and to have a serum bilirubin of 1.88 mg. %, of which 1.33 mg. % was indirect-reacting bilirubin. All other liver-function tests were within normal limits. A mild reticulocytosis occurred. All of these findings cleared promptly, and the hematocrit gradually returned to normal values. Since this patient had a complicating pneumonia, the hemolytic episode could not be ascribed unequivocally to the influenzal infection.

Serologic Determinations: The serum was examined for agglutination titers in 32 patients and found to be within normal limits for heterophil, typhoid O, typhoid H, paratyphoid A, Proteus OX-K, and Bru-

cella abortus. The level of cold agglutinins did not become elevated in the 7 patients in whom such determinations were made, nor did the antistreptolysin "O" titer change in the 16 patients in whom this test was serially performed.

Hepatic Function: Approximately one-third of the patients (25) were subjected to a series of liver-function tests, which included cephalin flocculation, thymol turbidity, serum bilirubin partition, total protein and albumin globulin ratios, total cholesterol, alkaline phosphatase, prothrombin time, and excretion of sulfobromophthalein (Bromsulphalein). With the exception of three patients who exhibited impaired excretion of sulfobromophthalein, all tests were within normal limits. Impaired dye excretion at 45 minutes (9% to 11%) was noted in two patients with simple influenzal infection and one patient (12%) with Klebsiella pneumonia and history of excessive alcohol ingestion in the past. One of the first two patients mentioned above had a serum glutamic oxalacetic transaminase of 60 Karmen units. There was no other evidence of hepatic disease in any of these three patients at the time of evaluation. A single patient with influenzal encephalomyelitis complicated by pneumonia experienced a mild hemolytic episode, with transitory elevation of the total and of the indirect reacting bilirubin.

Renal Function: Blood urea nitrogen, measured in 52 patients, was within normal limits. In one patient, who had a past history of prostatic surgery and probable chronic pyelonephritis, the level was 23 mg. %. The excretion of P. S. P. was normal in the 10 patients so tested. Routine urinalysis performed on all patients at the time of admission indicated a trace or 1+ albuminuria in eight patients with uncomplicated influenzal infection and seven patients with a complicating pneumonic process. This was a transitory phenomenon that disappeared on the same or on the following day. One of the patients with pneumonia also presented pyuria and bacilluria. His urinary abnormalities disappeared with appropriate therapy. Three of the patients with pneumonia exhibited a trace of acetonuria on admission, which was also noted to disappear later on the same day with hydration and supportive treatment. Finally, a single patient with influenza complicated by rheumatic pancarditis and congestive heart failure presented a trace of albuminuria at the time of admission.

Bacteriology: Blood cultures were negative in 35 patients with influenzal infection uncomplicated by pneumonia and in 11 of the patients with associated pneumonia. In the latter group there was one patient with a single blood culture which yielded Staphylococcus pyogenes var. aureus, thought to represent contamination. Cultures of the urine were negative in 14 patients. In 43 patients smears and cultures of the sputum and nasopharynx were obtained on one or more occasions. β-Hemolytic streptococci were cultured from the throat of one patient with typical streptococcal tonsillitis and of two patients with no clinical evidence of streptococcal infection. Of nine pneumonia patients in whom such studies were performed, Klebsiella pneumoniae and Diplococcus pneumonia were each noted in a single patient, on both direct and cultural examination of the sputum. A third patient presented innumerable staphylococci on initial examination of the sputum. Normal bacterial flora were obtained from the remaining 37 patients. It should be noted that these studies were, for reasons beyond our control, obtained in routine hospital care and do not represent extensive or specially directed bacteriologic examination. In fact, the hospital was least prepared to perform adequate bacteriological studies when the influenza epidemic reached New Orleans. This represents the influence of the antibiotic era.

Serum Enzymes: The serum glutamic oxalacetic transaminase (SGOT) was determined in 20 patients from 36 to 72 hours after the onset of illness and found to be within normal limits. Similar results were noted when the serum glutamic pyruvic transaminase levels were simultaneously

measured in 11 of these patients and in 6 patients in whom these determinations were repeated during convalescence. In one patient with uncomplicated influenza the SGOT measured 60 Karmen units. This patient also had a 45-minute retention of sulfobromophthalein of 9%. There was no other clinical or laboratory evidence of hepatic disease.

Blood Chemistry: In eight patients so examined, normal values were obtained for serum, calcium, phosphorus, and amylase. However, in 4 of 41 patients, in whom the fasting blood sugar was determined on the morning after admission, relative hypoglycemia was noted (56-59 mg. %). All were in the late months of pregnancy. Hyperglycemia was not encountered.

Fluid and Electrolyte Studies: The carbon dioxide-combining power was mildly reduced in 3 of the 24 patients in whom such determinations were made. These three, who also exhibited minimal elevation of serum chlorides, had pneumonia and exhibited tachypnea at the time of electrolyte alterations. There were 27 patients with normal serum chlorides.

Cerebrospinal Fluid: Lumbar puncture was performed in five patients. In no instance did culture of the spinal fluid reveal viral or bacterial growth. In four of the patients, all manometric, microscopic, and chemical determinations were within normal limits. The fifth patient, who presented a severe meningoencephalitic syndrome, exhibited elevation of spinal fluid pressure (220 mm. of water), increased cell count (270 lymphocytes), and abnormal protein content (70 mg. %). These abnormalities disappeared with convalescence and recovery.

Fluid and Electrolyte Studies in Twenty-Four-Hour Urinary Specimens: Urinary excretion of 17-hydroxycorticoids and 17-ketosteroids was measured in 14 patients at the height of illness and during convalescence.* In 1 patient only a single determination was made (at the height of illness), but the remaining 13 patients had from two to four such determinations. In every instance the excretion of urinary 17-hydroxycorticoids was within normal limits. In three patients the excretion of urinary 17-ketosteroids was increased during the 24-hour period at the height of illness. Two of the patients were women with uncomplicated influenza, whose peak excretion of 17-ketosteroids was 21.8 and 20.5 mg. in 24 hours, respectively. The third patient, with staphylococcal pneumonia (male), excreted 27.1 mg. of 17-hydroxyketosteroids during the 24-hour period at the height of illness. By the following day all values had returned to normal in all patients.

Respiratory Rate: Of 54 patients whose hospital records were sufficiently complete and accurate to permit evaluation of the respiratory rate, 21 patients were noted to be tachypneic. The reasons for an increased respiratory rate in these patients were usually complications of influenza, i. e., pneumonia (11), congestive heart failure with underlying rheumatic heart disease (2), bronchial asthma (2), acute laryngotracheobronchitis (1). Of five patients with simple influenzal infection who experienced tachypnea, two were in the ninth month of pregnancy. None of the simple influenzal patients experienced dyspnea. Tachypnea was limited to the first 72 hours of hospitalization and, except as noted below, was generally of the same intensity in all patients, i. e., an elevation of approximately 50% of the basic or convalescent respiratory rate (27-30 respirations per minute versus 18-20 respirations per minute). No appreciable difference in duration of altered respiratory rate was noted in this group of patients. However, there were four patients with pneumonia who exhibited respiratory rates greater than the figures quoted above. In three instances these rates were 75% to 100% greater than the normal rate of respiration. The fourth patient was noted, incident to pneumonia, term pregnancy, and acute pulmonary edema, to have a peak re-

* Performed by Dr. Joseph Dingman, of the Department of Medicine.

spiratory rate of approximately 60 per minute.

Fever: A diphasic or M-shaped fever curve was noted in 8 of the 15 patients with complicating pneumonia and 18 of the 61 patients with simple influenza.

In 60 patients with influenza uncomplicated by pneumonia the average duration of fever prior to admission was 1.5 days. In this group the febrile state during hospitalization lasted for 2.5 days and the average total febrile period was 4.5 days. A single patient with influenza complicated by acute rheumatic pancarditis was not included in these computations because of our inability to separate the influenzal syndrome from the acute rheumatic state. One of the patients with pneumonia complicating influenza also suffered from severe meningoencephalomyelitis and remained febrile for one month. The prehospitalization febrile state in the remaining 14 patients with influenza complicated by pneumonia was 2 days; the duration of fever during hospitalization was 4 days, and the average total febrile period was 6 days.

Pulse Rate: When the pulse rate differed by more than 10 beats per minute from the expected rate, i. e., 70-80 +10 beats per minute per degree of temperature elevation, disproportionate tachycardia or bradycardia was diagnosed. The observations reported below are limited to those observed in patients in whom there was no evidence of disease with or without complicating pneumonia and on whom adequate records could be kept.

Tachycardia: There were 73 episodes of tachycardia noted in 27 patients, the excess rate ranging from 12 to 54 beats per minute, with a mean of 19. Only one of these patients had coexistent pneumonia.

Bradycardia: There were 95 episodes of bradycardia observed in 38 patients. The pulse deficit ranged from 12 to 24 beats per minute, with a mean of 22. It is of interest that six of these patients had pneumonia. The latter group, although comprising slightly less than one-sixth of the study group, experienced more than one-fourth of all episodes of bradycardia observed. The degree and duration of bradycardia were essentially the same in patients with or without complicating pneumonia.

All instances of bradycardia were noted during the first 72 hours of hospitalization, usually within the first half of this period. It was uncommon to note the presence of bradycardia in the absence of fever. In contradistinction to the limitation of bradycardia to the acute phase of influenzal infection, tachycardia occurred only during convalescence. Approximately 85% of the patients who experienced tachycardia presented evidence of bradycardia earlier in the course of their illness, while only about 40% of the patients with bradycardia experienced tachycardia.

Blood Pressure: Only one instance of hypotension was observed. This was in a young man severely ill with staphylococcal pneumonia. At the time of admission to the hospital his blood pressure was 120/50 mm. of mercury in the supine position. On sitting he complained of faintness and was found to have a blood pressure of 95/40 and a pulse rate of 124 beats per minute. During the next 24 hours, although his systolic pressure remained essentially unchanged, the diastolic pressure ranged from 30 to 60 mm. of mercury. This was the only patient in whom rheoplethysmographic studies performed at the peak of illness revealed digital vasodilatation and increased digital blood flow.

Hypertension was noted in five patients. In three of these, the hypertension was noted when anxiety and pyrexia were most pronounced, i. e., during the first 24 to 48 hours of hospitalization, at the height of illness. The systolic blood pressure was slightly elevated (10 to 15 mm. Hg), with little or no change in the diastolic pressure. During the same period of their illness, the other two patients had slightly greater alterations in blood pressure; i. e., the systolic pressure rose 15 to 20 mm. Hg and the diastolic 10 to 20 mm. Hg.

Circulatory Studies: The circulation time and venous pressure, determined on at least

one occasion in 12 patients, were within normal limits. In two patients, with obvious congestive heart failure and underlying rheumatic heart disease, systemic venous pressure was elevated, although the circulation time was within normal limits.

Associated Clinical States.—Pregnancy: There were 13 pregnant patients in this study (approximately 17%). All were multiparous and in the second (3) or third (10) trimester of pregnancy. In six patients, pregnancy continued unaffected by the respiratory infection. There were four instances of full-term, normal, spontaneous delivery, although in one of these the child died on the ninth day of life. Postmortem examination revealed pulmonary hemorrhages, thought to be due to influenzal infection, intracerebral hemorrhage, and leptomeningitis. Attempts to recover bacterial or viral organisms were unsuccessful in this case just as in the two fetal deaths. These followed 36 hours and 6 hours of labor during the sixth and seventh months of pregnancy. Postmortem examination revealed diffuse hemorrhagic interstitial pneumonitis in one instance and intracerebral hemorrhage and atelectasis in the second.

Thus, of 13 pregnancies complicated by influenzal infection, 3 terminated in the death of the infant. Of these, only one was associated with any complication of influenza, i. e., pneumonia and mild toxemia. The latter was minimal and appeared to be unaffected by the viral infection. The pregnant patients appeared to be more seriously ill with the influenzal infection than were the nonpregnant patients. However, it must be noted that the pregnant patients in this series sought medical care because of the severity of their symptoms and thus constitute a selected group.

Cardiac Disease: Simple influenzal infection precipitated congestive heart failure in two women with mitral stenosis due to rheumatic heart disease. Both of these patients, who were in their fourth decade, experienced recurring episodes of acute pulmonary edema, resulting in hospitalization. Appropriate therapy prevented further attacks and resulted in the disappearance of the clinical signs of congestive heart failure.

A single teen-aged girl who was initially hospitalized for severe influenza, was found to be suffering from severe rheumatic pancarditis at the time of admission. She had had previous episodes of rheumatic carditis earlier the same year. Although desperately ill the patient made an excellent recovery. Paired sera revealed more than a fourfold rise in hemagglutination inhibition antibody titer. It was impossible to separate the influenzal from the rheumatic process clinically or to determine the exact etiologic significance of the viral infection. Clinical, bacteriologic or immunologic evidence of streptococcal infection could not be obtained in spite of intensive search.

There were two patients, in the seventh and eighth decades, respectively, who suffered from arteriosclerotic cardiovascular disease. Both suffered from pneumonia as well as influenza. One of the patients was on maintenance doses of digitalis. The cardiac status did not become worse in either patient as a result of respiratory infection. In fact, the only abnormality noted was the presence in one patient of numerous premature ventricular contractions at the time of initial examinations. These had disappeared by the following morning.

Bronchopulmonary Disease: Four patients had a history of asthma, all of whom characterized this ailment as mild and infrequent or rare in appearance. In two of these patients the peak of their influenzal infection was marked by dyspnea and wheezing which rapidly responded to bronchodilators and expectorants. The third patient, who suffered from concurrent pneumonia, was more dyspneic and presented a severer asthmatic picture. He too responded, but more slowly, to conventional therapy. The last patient, who also suffered from pneumonia, experienced acute pulmonary edema shortly after delivery. As mentioned elsewhere, it is impossible to evaluate the significance of asthma in the genesis of her clinical syndrome. Of interest is the fact that these patients all had extremely mild asthma and

had not experienced allergic symptoms for many years. This phenomenon suggests the extent of endobronchial alteration necessary to evoke an asthmatic response. There was one patient with moderately active pulmonary tuberculosis whose disease was unaffected by the influenzal infection. Only one other patient had a past history of chronic pulmonary disease, which included a right middle lobectomy for lipoid granuloma. At the time of surgery and during convalesence from the influenzal infection pulmonary-function studies revealed a mild ventilatory defect of essentially the same degree. This patient tolerated well his influenzal infection with superimposed pneumonia.

Neurological Disease: There was one elderly patient with amyotrophic lateral sclerosis who suffered from influenza complicated pneumonia. Although she experienced considerable difficulty in expelling secretions from her endrobronchial tree, she responded satisfactorily to expectorants, bronchodilators, and antibiotics.

Genitourinary Disease: One pregnant woman was found to be suffering from a mild case of cystitis, which rapidly cleared with antibiotic therapy. An elderly white man with a past history of transurethral surgery for benign prostatic hypertrophy and probable chronic pylonephritis was found to have pyuria and a blood urea nitrogen level of 25 mg. %. Antibiotic therapy for influenza-associated pneumonia resulted in disappearance of the abnormal urinary findings. Unfortunately, the patient deserted the hospital before blood-chemistry determinations could be repeated.

Metabolic Disease: There was only one known diabetic in the study group. His diabetes was mild and unaffected by the influenzal infection.

Rheoplethysmography: Sixteen of these patients had digital rheoplethysmographic studies by methods previously described.[1] The results of these studies have been presented in detail. Briefly, reduction in digital blood flow occurred at the height of illness in most patients. The degree of reduction in rate of digital blood flow correlated well with the severity of illness and disappeared with convalescence. A single patient, previously mentioned, who suffered from staphyloccal pneumonia and presented transitory hypotension, was the only patient in whom digital vasodilation was present at the peak of influenzal infection. In all instances digital vascular responses to the usual stimuli were essentially normal.

Electrocardiography: The results of the specially directed investigation of the influence of Asian influenza on the cardiovascular system have been reported.[2] Of 36 influenzal patients subjected to routine electrocardiography, 10 had abnormal tracings. Thirteen of sixteen additional patients studied with serial electrocardiographic examinations presented transient alterations. Sinus bradycardia, prominence of the P-waves, minimal ST segment, depression, and right axis deviation were each encountered once. In all other patients the alterations were limited to T-wave changes. Clinical evidence of myocarditis was not encountered.

Spatial Vectorcardiography: Fourteen of sixteen patients studied with serial spatial vectorcardiograms showed irregularities in the contour of the QRS ₛE-loop, consistent with alterations in the process of depolarization. This may indicate that with sufficiently sensitive recording of the process of depolarization, it is altered readily by infection. In six instances these disappeared with convalescence. Four of the patients showed slight transitory arching of the efferent limb of the loop, similar to that observed in diaphragmatic myocardial infarction.

Complications.—In this group of 76 patients, 15 had pneumonia and 1 each had β-hemolytic streptococcal pharyngitis, acute laryngotracheal bronchitis, purulent conjunctivitis, and meningoencephalomyelitis. The latter complication was associated with what appeared to be a mild hemolytic anemia. Two additional patients were found to harbor asymptomatically β-hemolytic streptococci. Acute rheumatic pancarditis (one patient), acute pulmonary edema (one

patient), and congestive heart failure (two patients) were also encountered. All responded to conventional therapy and were free of sequelae.

Treatment.—Of the 61 patients with influenza uncomplicated by pneumonia, 21 received antibiotic therapy. In 15 instances this was prophylactic in purpose and did not appear to alter the course of the influenzal infection. In the remaining cases, this form of treatment was prompted by the presence of a bacterial complication (purulent bronchitis, 2), (asthma and bronchitis, 1), (acute laryngotracheobronchitis, 1), (purulent conjunctivitis, 1), and (streptococcal pharyngitis, 3).

Thirteen of the fifteen patients with pneumonia were treated with penicillin supplemented in all but one instance by one or more antibiotics. These consisted of streptomycin (9), oxytetracycline (Terramycin) (4), chloramphenicol and erythromycin (1). In the latter case, because of clinical toxicity and the presence of many staphylococci on examination of the stained sputums, the patient was given 40,000,000 units of aqueous penicillin daily for the first three days of treatment and supplementary probenecid throughout the course of treatment. Two patients were treated solely with tetracycline (Achromycin). There were no untoward reactions to the antibiotics, and the response was satisfactory in all cases.

Steroids were given to one patient who experienced acute pulmonary edema only 24 hours after the onset of her illness. She had a past history of asthma and presented generalized wheezing, rhonchi, and fine moist rales at the peak of her illness. Since her condition appeared desperate she was digitalized with intravenous lanatoside (Cedilanid) and given parenteral cortisone in addition to the usual measures, consisting of oxygen, bloodless phlebotomy, bronchodilators, and expectorants. Her response to therapy was dramatic, but no single aspect of the treatment program could be adequately evaluated.

Comment

Inconstancy of clinical forms, variability of complications, and sporadicity of sequelae combine to make influenza an ill-defined syndrome of protean manifestations. Every pandemic is initially viewed as a new form of disease. Eventually laboratory and epidemiologic data indicate the nature of the infection and demonstrate its unity with the great influenzal pandemics of the past.

One feature is common to the literature concerned with influenza. It is the disagreement between various authors as to the clinical picture, severity, complications, and sequelae of any single epidemic or any series of epidemics or pandemics.[3-22] This is further compounded by serial observations of single persons who note the differences between successive epidemics or pandemics with which they have had intimate contact and extensive experience. Thus, Turner,[23] Stengle,[24] and Craig,[25] each of whose experience encompassed almost four decades of influenza in all its forms, repeatedly noted the variation in epidemics and pandemics. Stuart-Harris,[26] with similar experience but armed with more precise diagnostic techniques, reaffirmed these conclusions. The reports of individual observers, dealing with the same epidemic, indicate intraepidemic variations.[27,28] Finally, reports of isolated sporadic epidemics reveal striking similarity or variance with previously reported outbreaks.[29,30] If one were so inclined, it would be possible to liken Asian influenza to the pandemic of 1889-1890 in its mildness, variability and paucity of complications, and low morbidity but to note its dissimilarity in lack of neuropsychiatric and otorhinolaryngolic complications. Similar comparisons could be made to each epidemic and pandemic. It would appear that the availability of antibiotics in this pandemic probably reduced the incidence of complications and deaths.

The data presented in this report attain significance only by virtue of occurrence in patients demonstrated by reliable laboratory methods to be suffering from influenzal

infection. No claim can be made that all symptoms, findings, or alterations in body functions result from infection with the virus of Asian influenza. As demonstrated by Horsfall,[31] infection with the influenza virus may be attended by insignificant clinical manifestations but diagnostic laboratory findings. However, it is only by the careful study of proven cases that we will understand influenzal infection.

Summary

Data derived from the intensive clinical study of 76 proven cases of Asian influenza are presented. The presence of preexisting cardiac disease or pregnancy frequently aggravated the usual mild to moderate severity of the infectious process. Occasional uncommon or severe complications and a high incidence of electrocardiographic abnormalities were noted. However, permanent sequelae were not encountered.

This study, in addition, describes for the record in a series of serologically or virologically proven cases the clinical manifestations of the recent pandemic of Asian influenza, especially as noted in the New Orleans area.

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Blood Cholesterol and Uric Acid of Healthy Medical Students Under the Stress of an Examination

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The examination of medical students at the end of their course of studies offers an opportunity to investigate physiological changes occurring in an emotionally stressful situation in healthy persons. Under such and similar circumstances eosinopenia [1-4] and accelerated coagulation [5,6] have been demonstrated.

On close study of the life histories of a number of patients with coronary occlusion it has been found that mounting emotional stress frequently preceded such an event [7,8]; it was in a number of instances complicated by an acute additional stressful experience close to the occurrence of cardiac infarction. The similarity of this sequence of events with the situation of preexamination tension terminating in the stress of the examination itself prompted us to study the level of blood cholesterol and its fractions bound to α- and β-lipoprotein under these circumstances. Since a number of patients with coronary artery disease exhibit hyperuricemia, and since stress and corticotropin are apt to increase uric acid excretion, uric acid blood levels were also measured.

Material and Methods

Twenty-one healthy medical students, eighteen men and three women, served as subjects of this investigation. The cholesterol, its α- and β-lipoprotein fractions, and the uric acid level of their blood were determined on two occasions, first on the morning of their final examination in medicine, when they had already studied a patient assigned to them but were just expecting to undergo the oral examination, and second about 48 hours later. The only criterion in selecting these students from a group of 30 was their availability for the second or "control" test.

Blood cholesterol was estimated by the method of Anderson and Keys.[9] The error of this estimation was ±3% in our laboratory. Uric acid was determined by the method of Hepler and Stoskopf.[10] β-Lipoprotein-cholesterol was determined by paper electrophoresis and elution of the cholesterol from the respective part of the paper strip. α-Cholesterol was then calculated by subtracting β-cholesterol from total cholesterol.

Results

The Table and the Graph demonstrate that total serum cholesterol values were higher, though, with one exception, also well within the range of normal, on the day of examination in 20 out of 21 students than on the day of the control test. In one student (Student 17) the values were practically equal on both occasions. The additional amount of cholesterol found on the day of the students' examinations appeared mostly in the α-fraction, although —taking the limitations of technique into proper consideration—these results are not entirely conclusive.

Uric acid levels are fairly constant when one compares the results of the two series of tests. The Table contains also the statistical evaluation of the results pointing to a significant difference in cholesterol between the two series.

Comment

Although the result of this investigation, as expressed in figures, is largely unequivocal, its interpretation is by no means obvious.

The behavior of serum cholesterol after administration of corticotropin and corti-

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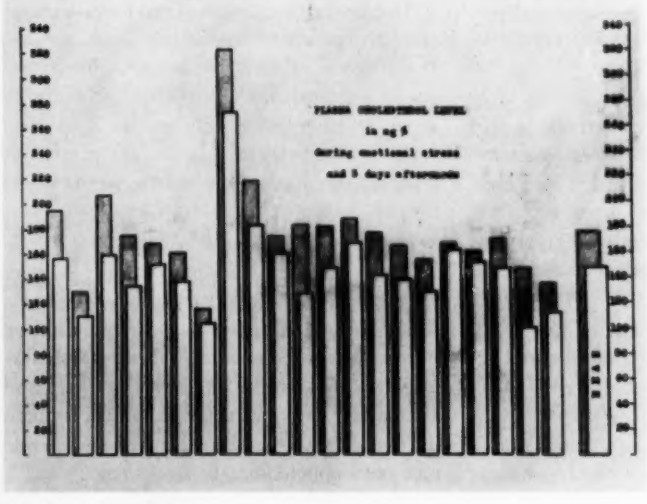
Plasma Cholesterol, β-Lipoprotein Cholesterol, and Uric Acid Values of Twenty-One Medical Students During and Two Days After Examination and Statistical Evaluation *

Student	Plasma Cholesterol Level			Cholesterol in Plasma β-Lipoprotein Fraction, Mg. %		Plasma Uric Acid Level, Mg. %	
	I, Mg. %	II, Mg. %	III, %	I	II	I	II
1	195	156	+25	123	119	4.5	5.4
2	130	115	+13	86	84	5.0	5.3
3	206	159	+30	111	105	4.2	4.3
4	175	134	+31	90	87	4.8	5.0
5	168	151	+11	135	107	6.9	6.5
6	160	137	+17	50	71	6.3	5.6
7	116	104	+11	95	90	6.5	5.8
8	322	272	+18	228	205	5.2	5.2
9	217	182	+19	164	166	6.2	6.4
10	173	160	+ 8	92	133	5.8	6.6
11	182	128	+42	105	115	6.3	5.7
12	181	148	+22	85	105	4.2	4.3
13	187	168	+11	151	157	4.4	4.5
14	176	142	+24	82	87	4.2	4.0
15	165	138	+20	83	91	4.1	3.5
16	154	129	+19	91	84	5.5	4.8
17	167	162	+ 3	84	91	4.3	4.1
18	161	150	+ 7	90	98	7.4	7.0
19	171	147	+16	76	91	5.3	5.2
20	147	100	+47	97	109	7.4	7.2
21	135	112	+20	80	91	4.9	4.7
Mean	(176)	(143)	(+20)	(105)	(109)	(5.4)	(5.3)

* I indicates during examination; II, 2 days after examination; III, percentage increase of examination values (I) over controls (II). Statistical values: Mean diff. in %, +20; S. D. of diff., 19.7; *t*-value, 8.2; *P*-value, <0.001.

costeroids has shown various trends, as was recently pointed out by Adlersberg.[11]

The results of animal experiments concerning the effect of stress, corticotropin, and the corticosteroids are equivocal. Various animal species react differently to the administration of these substances; rabbits and rats respond with an increase in blood cholesterol,[12-16] whereas dogs exhibit either no rise or a small one.[14] Adlersberg and his co-workers [17] observed an increase not infrequently in serum cholesterol in patients



Results of blood cholesterol determination in 21 medical students obtained on the day of their final examination in medicine and two days afterward.

on cortisone and corticotropin (ACTH) treatment. Conn with his co-workers,[18,19] on the other hand, described an initial decrease of cholesterol after corticotropin administration in normal persons, a situation also observed by Oliver and Boyd[20] in "men with high plasma cholesterol and coronary artery-disease." Barr[21] described the changes he had observed in normal persons as inconstant. Mann and White[22] concluded that experimental stress would actually decrease blood cholesterol in dogs and rats and prolonged and severe disease would do the same in men.

It is consequently not so obvious as it may seem at first that the higher "examination" value of cholesterol represents an increase over the "control" level as determined two days afterward. Theoretically, at least, the reverse relation cannot be excluded. Only a number of further control tests, unfortunately impracticable under the circumstances, could settle this question definitely. We feel, however, that the first value has to be regarded as the one increased over the control value for the following reason. In our previous investigations[2,6] it was always the "examination" value which clearly presented the deviation from the normal, be it the absolute eosinophil count, blood pressure, or clotting time. This certainly points to the stress action—corticotropin-like in its effect—of the examination situation and marks the findings then obtained as the results of the stimulus.

The uric acid blood level shows no large differences; renal clearance methods should probably be used to observe stress influence with a more sensitive method. However, employment of this method, even in an abbreviated form and related to creatinine clearance, has its practical drawbacks in the situation tested.

It is difficult to evaluate our finding of an increased serum cholesterol as to its implications as a stress response. It remains an open question whether this represents mobilization of cholesterol as a potential source of adrenal steroid hormones required in order to cope with the stimuli of the situation of tension.

Recent work tends to implicate an increase in blood fats in the induction of a state of hypercoagulability.[23-25] Such accelerated clotting, as already mentioned, has been shown to be a response to various stimuli including emotional stress, as in the situation examined here. Following our present investigation it would be of interest to study elderly persons, especially those who are certainly affected by coronary atherosclerosis, for their blood cholesterol levels when they are under the influence of stressful life experiences.

The stress reaction here elicited through an emotional stimulus expresses itself in decrease in clotting time, rise in blood cholesterol, and further through a decrease in blood eosinophils. Such a combined response may thus set the stage for the development of coronary or other thromboses. Whether transient rises in the blood cholesterol level per se contribute to the development of atherosclerosis is as yet a matter of conjecture. The finding presented here evidently poses a number of questions which should stimulate further research both in thrombogenesis and atherogenesis.

Summary

The final examination of students in medicine represents a model situation for the study of the effect of an emotionally stressful life experience. With the intention to learn whether blood cholesterol and uric acid vary significantly under these circumstances, 21 medical students were investigated.

In 20 students serum cholesterol levels were higher, within the physiological range, during the examination than they were in a control test taken two days later. The α-, β-lipoprotein distribution of blood cholesterol seemed to show that the increased amount of cholesterol tended to accumulate in the α-fraction. Blood uric acid levels remained approximately unchanged.

These findings are discussed in relation to the development of coronary thrombosis and atherosclerosis.

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The Hebrew University Hadassah Medical School (Dr. Dreyfuss).

Addendum

Since this study was submitted for publication, a paper by Drs. C. Bedell Thomas and E. A. Murphy has appeared in the *Journal of Chronic Diseases* (8:661 [Dec.] 1958) dealing with an almost identical situation. Their results as to total blood cholesterol and blood eosinophils closely resemble ours.

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Nocardia Asteroides Infection

A Report of Seven Cases

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Introduction

Nocardiosis is a granulomatous and suppurative infectious disease which is caused by the aerobic actinomycete Nocardia asteroides. Manifestations may be acute or chronic, localized, or generalized. Diagnosis is dependent upon laboratory identification of the fungus upon its recovery from involved tissues. Reports of cases of nocardiosis appear with increasing frequency, yet they remain relatively uncommon, which would suggest that the disease is rare or, more likely, unrecognized.

It is the purpose of this paper to describe seven additional cases of this infection, all studied and treated at the Memorial Center for Cancer and Allied Diseases between the years 1952 and 1957. Particular attention is called to the presence of complicating neoplastic disease in five of the seven patients afflicted.

The data presented here include also the results of tests of sensitivity to several antibiotics in vitro, as well as detailed characterizations of the strains recovered, despite the fact that antibiotic therapy, when used alone, displayed discouraging limitations in the treatment of nocardiosis, even in instances when a high degree of activity was demonstrable in vitro. Such characterizations of the strains appear, however, to permit more complete bacteriological differentiation among strains, an observation which should prove valuable to future studies.

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An extensive review of the mycology, pathology, clinical patterns, and approaches to treatment has been omitted, since these features have been adequately discussed by other writers, to several of which attention is directed.[1-6]

A synopsis of our seven cases is presented in Table 1. The salient features of each case history now follow, together with comments which illustrate various facets of nocardiosis.

Case Histories

CASE 1.—A 36-year-old woman presented herself because of a progressively enlarging breast mass, first noticed two weeks previously. Of especial interest was her recollection that two years earlier she inadvertently abraded the breast upon a rosebush thorn in her garden. Physical examination disclosed only a 5×7 cm. firm, tender mass, with overlying tissue inflammation, and nipple retraction.

Aspiration of the lesion resulted in purulent material which contained many leukocytes and a moderate number of beaded, Gram-positive, branching structures morphologically compatible with an actinomycete.

Incision and drainage of the breast abscess were done, and treatment with tetracycline instituted, which was continued for four weeks. Despite antimicrobial therapy an indurated sinus tract and recurrent abscess developed which necessitated a wide local excision two months after the initial procedure. Nocardia asteroides were still recovered from this specimen upon culture, and the organisms were seen in suitably stained sections. Postoperatively, she received tetracycline, penicillin, and isoniazid. Wound healing was prompt following this more extensive and definitive surgery.

Comment.—Interest in this case of nocardiosis lies in the anatomic site of involvement, previously unreported—the breast—and the likelihood that infection was exogenously introduced by a rose-thorn abrasion. This situation is reminiscent of mycetoma, a deep tissue and bone infection most often

encountered in a lower limb of those who live barefooted. Surgical extirpation, not antibiotic therapy, was credited with the cure in this case.

CASE 2.—A 41-year-old chronic alcoholic and heavy smoker was admitted because of chronic cough productive of abundant, thick, yellow, blood-streaked sputum. These symptoms were the residua of a severe pneumonia diagnosed and treated with injections five weeks previously by an outside physician. The patient had a further history of a pneumonia two years earlier.

The significant findings were in the chest, both by auscultation and roentgenogram, the latter on admission showing patchy and streaky densities in the right lower lobe, less pronounced than those present on a film taken elsewhere 10 days before. Bronchoscopy revealed a hyperemic bronchial mucosa. Neither malignant cells nor tubercle bacilli were recovered from bronchial washings.

He was observed as an outpatient for three months with no change other than the appearance of clubbing of the fingers. Bronchoscopy was repeated which showed foul-smelling exudate to issue from the right bronchial tree. The washings were again negative for malignant cells and tubercle bacilli.

A right lower lobectomy was performed. The specimen showed a large cystic cavity occupying the hilar portion of the lobe. Microscopically, the pathologist observed organizing bronchopneumonia, bronchiectasis, and lung abscesses. A sputum which was obtained just prior to surgery and submitted to the bacteriologist for routine culture grew, postoperatively, N. asteroides.

After the operation he received penicillin and streptomycin for five days, and then oxytetracycline for the ensuing two months. Follow-up examinations over a period of six months, including sputum cultures for the detection of Nocardia, showed no evidence of recurrence.

Comment.—Although it is probable that Nocardia may be saprophytic, along with many other micro-organisms in chronic lung abscesses and bronchiectasis, its earlier detection might have been effected, and possibly therapy altered, had the sputum specimens been submitted to the bacteriologist with a request for "routine" and fungus, as well as acid-fast cultures. Nocardia are less hardy and rarely survive the rigorous concentration techniques employed upon specimens which are to be cultured for tubercle bacilli.

In this instance, being apprised of the bacteriologic finding, the pathologist restained the tissue sections, using a modified Gram-technique (Brown and Brenn). Inspection then of these tissue sections showed Gram-positive branching forms compatible with actinomycetes in the borders of the pulmonary abscesses and invading the lung parenchyma, thus establishing beyond doubt that Nocardia played at least a partial role in causing the destructive lesions.

It is important to note that specific identification of the actinomycete in pulmonary tissue is usually not possible with hematoxylin and eosin tissue stains. Modified Gram techniques must be employed, which are generally not routinely carried out. Occasionally acid-fast stains suffice. In sputa and drainage materials a smear, stained by Gram's method and carefully searched, will usually display the hyphae of the actinomycetes.

Cure in this case is attributed to surgery. The role the antimicrobials played in the possible suppression of infection, or in curbing its spread, cannot be evaluated.

CASE 3.—A 3-year-old boy had been treated elsewhere with cortisone for acute leukemia of five months' known duration. Tetracycline had been employed several times as infectious complications arose.

On admission to Memorial Center he was moderately febrile and presented hepatosplenomegaly, generalized peripheral adenopathy, anemia, and leukopenia. A bone marrow aspiration was diagnostic of acute leukemia.

His course during the succeeding four months was rapidly downhill, despite treatment with prednisone, mercaptopurine, amethopterin, tetracycline, and chloramphenicol. In this interval many of the stigmata of progressive acute leukemia were in evidence, including fever, hemorrhagic tendencies, marked leukopenia, and repeated respiratory infections.

Autopsy disclosed widespread leukemic infiltrates in various organs. Of especial interest was the presence of a 1 cm. grayish-yellow subpleural abscess in the right middle lobe of the lung. Microscopically, the lungs showed focal bronchopneumonia with abscess formation. A smear of the right lung tissue showed many Gram-variable beaded filamentous long rods, some of which branched. On culture these were identified as N. asteroides. No cultures of other tissues or blood produced the organism.

Comment.—In this instance, the diagnosis of pulmonary nocardiosis was made after

TABLE 1.—*Synopsis of Case Histories*

Case	Age, Yr.	Sex	Clinical Features	Management	Mycologic Diagnosis	Chemotherapeutic Agents Employed	Therapeutic Result
1	36	F	Acute breast abscess, 2 wk. duration	Incision and drainage; postoperative antibiotics	Branching forms compatible with actinomycetes seen in smears of purulent exudate	Postoperatively: procaine penicillin, 300,000 units b. i. d. × 3 days; tetracycline 1 gm/day ×5 days; then 2 gm/day ×4 wk.; potassium iodide 3 wk.	Sinus formation; persistent pain & induration; therapy considered ineffectual; progressive indolent disease
			4×6 cm. dense fibrous, chronic breast abscess	Wide surgical excision; postoperative antibiotics	N. asteroides by smear & culture	Postoperatively: procaine penicillin 600,000 q. d. ×2 wk.; isoniazid 400 mg/day ×2 wk.	Surgical cure
2	41	M	Acute pneumonia, cough with thick yellow & blood-streaked sputum; incomplete resolution	At home; antibiotics		Penicillin (? amount)	Progression to chronic suppurative pulmonary infection, observed 5 mo.
			Residual chronic suppurative right lower lobe pneumonia & lung abscess; duration 5 mo.	Lobectomy	N. asteroides by culture of preoperative sputum specimen & forms compatible with actinomycetes in lung sections	Postoperatively: penicillin, 300,000 units q. d. ×5 days; streptomycin 1 gm/day ×5 days; oxytetracycline (? 1-2 gm/day ×2 mo.)	Surgical cure; Nocardia not subsequently cultured from sputum
3	3	M	Acute leukemia, diagnosed during attack of acute tonsillitis 5 mo. before death; fever & hemorrhagic tendency predominant; chest roentgenograms considered normal	Antileukemic therapy, including prednisone from 9th to 2d wk. prior to death, and corticotropin for terminal 3 wk.	In autopsy material; tissue sections of right lung showed many branching forms consistent with actinomycetes; culture positive for N. asteroides	Chloramphenicol 1 gm/day ×8 wk.; tetracycline 1 gm/day ×1 wk.	Death from leukemia; N. asteroides present and viable in lung tissue despite antibiotic therapy; no evidence dissemination to left lung, liver, spleen, brain
4	45	M	Chronic myelogenous leukemia, 2½ yr.	Radiation, potassium arsinite solution, prednisolone, (busulfan) Myleran, mercaptopurine		Penicillin & intermittent courses of tetracycline & nystatin used prophylactically over 2 yr. interval	Ultimate entry into acute phase myelogenous leukemia
			Acute myelogenous leukemia; generalized mucosal moniliasis; hectic febrile course, 3 wk.; tracheostomy of necessity, with purulent wound infection; terminal pneumonitis, 4 days	Supportive, prednisone, & 6-chloropurine	Admission blood cultures negative; Nocardia isolated twice on separate occasions during week prior to death from blood cultures drawn before starting antibiotics; organism not obtained from trachea or tracheostomy wound	Chloramphenicol, 2 gm/day; novobiocin, 2 gm/day; erythromycin, 1 gm/day ×6 days prior to death	Death; hectic course ascribed to pneumonia, no further blood cultures taken; post mortem refused; locus of invasion of Nocardia unknown; ? lung

5	47	F	Cancer of breast, progressively metastatic over 12 yr. to pleura, skin, bones, peritoneum; arrest of disease process after hypophysectomy performed 5 mo. prior to final admission; terminal episode one wk. in duration; clinical diagnosis — intracerebral lesion, posterior cranial fossa, presumably metastatic cancer; coma, temperature 110 F	Over 12-yr. span: Irradiation castration; sex hormones; prednisone 5 mo. prior to death: P^{32} intra-abdominally; hypophysectomy; thoracentesis Terminally: Irradiation of skull; intravenous HN_2	In autopsy material; multilocular cerebellar abscess; N. asteroides obtained in pure culture, & identified in histologic sections of brain lesion	No antibiotic agents	Death caused by brain abscess, due to N. asteroides; cancer in remission; no tumor metastases in brain
6	39	M	Acute lung abscess, due dually to N. asteroides and D. pneumoniae Type XIII; infection developed nearly asymptomatically in patient during metabolic study after 18 mo. cortisone therapy for well-controlled chronic leukemia	Cortisone withdrawn; antibiotic therapy for 6 wk.	Smear & culture of sputum	Preoperatively: Aq. penicillin 100,000 q. 3 h. ×6 days; penicillin aerosol × 5 wk.; chlortetracycline, 1 gm. q. 4 h. ×6 days, then 1 gm. q. 6 h. ×4½ wk.	Rapid clearance of D. pneumoniae, suppression of Nocardia in sputum and roentgenographic improvement for 4 wk.; then, mycologic & roentgenographic relapse & spread
			Chronic lung abscess & spreading pneumonitis	Left upper lobectomy	Extirpated left upper lobe teaming with Nocardia in original abscess area as well as in fresh areas of infection; presumably bronchogenically spread	Postoperatively: chlortetracycline; 1 gm. q. 6 h. ×2 wk.; chloramphenicol 1 gm. q. 6 h. ×2 wk.; 0.5 gm. q. 6 h. × 2 wk.	Surgical cure; Nocardia never again recovered from pt. or at autopsy, 19 mo. later; death from leukemia & sepsis other than Nocardiosis
7	37	F	Hodgkin's disease, 14 yr.	Radiation therapy; corticosteroids			Moderate success until infectious aspect dominated picture during last 5 mo. of life
			Systemic Nocardiosis, manifested chiefly by lung abscess, diffuse & progressive pneumonitis; purulent arthritis; purulent otitis; progressive mental disturbance	Corticosteroids; numerous antibiotics; supportive therapy	Smear & culture during life from knee joint & ear & from numerous organs showing metastatic abscesses at autopsy	See Fig. 4 & Table 2; of all generally employed suppressive agents, sulfonamides alone were not employed in substantial amounts	Death due to disseminated Nocardiosis 5 mo. after detection of pulmonary lesion; progressive pulmonary disease; systemic spread while on therapy

death. The abscess was still small in extent and, if Nocardia were being liberated into the bronchus from the lesion, they were not detected, perhaps because of the difficulty in obtaining sputum from children. Several throat cultures were productive only of coagulase-positive Staphylococcus pyogenes var. aureus, which appeared to play no significant role in this instance.

In a patient with such a neoplastic disease, in whom the host parasite relationship appears to be radically disturbed and in whom steroid therapy is being employed, it is generally noted to be but a matter of time before far more extensive evidence of nocardiosis is found, provided death does not result first from leukemia. The possible beneficial effects of antibiotics in suppressing extension of nocardiosis cannot be estimated.

CASE 4.—A 45-year-old man with chronic myelogenous leukemia was referred to Memorial Center after a year of therapy elsewhere which included potassium arsenite (Fowler's solution), busulfan (Myleran), mercaptopurine, prednisolone, radiotherapy to the spleen, blood transfusions, and occasional courses of tetracycline.

On admission he was found to be seriously ill and febrile, with an anginose oropharynx, hepatosplenomegaly, and pancytopenia. Three cultures of venous blood taken on and shortly after admission were sterile, as was a spinal fluid culture.

Antileukemic therapy with 6-chloropurine and prednisone was instituted. On the fourth hospital day the oropharyngeal infection and laryngeal edema necessitated a tracheostomy. The tracheal aspirate yielded upon culture S. pyogenes var. aureus, coagulase-positive, Group D streptococci, Escherichia coli, and Pseudomonas aeruginosa.

The patient died three weeks after admission despite supportive care, antileukemic therapy, and the administration of chloramphenicol, erythromycin, and novobiocin. His entire course was severely septic, with the terminal development of bronchopneumonia, icterus, and vascular collapse.

N. asteroides was isolated from two of three blood cultures drawn on separate occasions during his last week of life. No postmortem examination was permitted, and the focus of entry of Nocardia into the bloodstream was not determined.

Comment.—This case is of interest in that Nocardia was isolated twice from the bloodstream, in the face of antimicrobial therapy considered suppressive by in vitro standards. Isolation of Nocardia from the blood is very unusual, even during obvious clinical dissemination by what must be a hematogenous route,[7] (see also Case 7).

CASE 5.—A 47-year-old woman was observed and treated throughout a 12-year period after radical mastectomy for carcinoma of the breast. During that time she slowly developed widespread metastatic disease, which, however, was successfully controlled for extended intervals by various means, including radiation therapy, surgical castration, and, for the terminal two years, prednisone.

Six months prior to death, a hypophysectomy was performed. Marked symptomatic improvement appeared to follow, including complete relief from skeletal pain.

Twelve days before her death an abrupt deterioration began with chills, myalgia, nausea and vomiting, lethargy, giddiness, and a sensation of retro-orbital fullness. Admission examination disclosed hyporeflexia and muscle weakness on the right side of the body, with dissociation of head and eye movements. A diagnosis of an intracerebral lesion of the posterior cranial fossa was made which was presumed to represent metastatic cancer. Despite heroic treatment she lapsed into deep coma. Her temperature rose unabated and reached 110 F, at which point death occurred.

At postmortem examination no tumor metastases were found in the brain but, remarkably, a multiloculated abscess cavity which contained greenish purulent material. The abscess, poorly encapsulated, replaced most of the white matter in the right cerebellar hemisphere and involved part of the cerebellar peduncle. Bacteriologic examination of the purulent material displayed N. asteroides in pure culture. Histologic sections prepared with Brown and Brenn stain also showed the organism within the abscess and adjacent brain tissue.

Comment.—This case epitomizes a most unexpected finding at necropsy, a brain abscess due to Nocardia instead of the anticipated metastatic cancer. As the case presented itself, no amount of diagnostic acumen could have served to foretell the facts. Nocardia was not isolated from any other site. One can only speculate in this case, as in others here presented who were treated with adrenal corticosteroids for extended periods, on the role of these agents in promoting dissemination of the fungus from the site of invasion. In this instance, metastatic breast cancer had not led, so far as is known, to disturbances of the host-parasite equilibrium, such as appear to exist in the leukemias and lymphomatous disease.

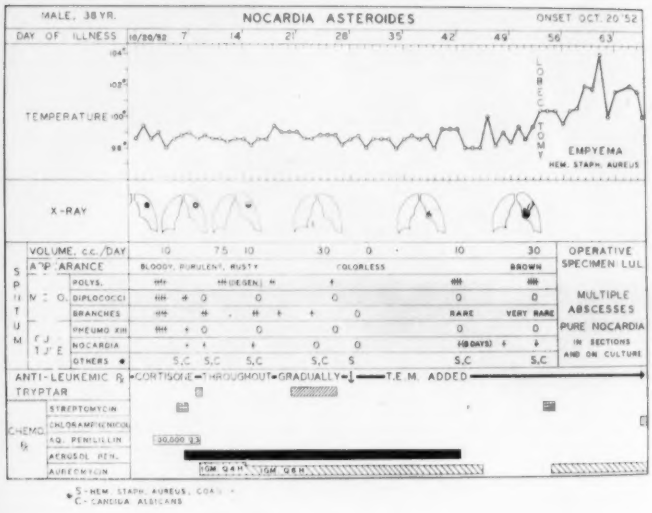


Fig. 1 (Case 6).—Acute lung abscess due jointly to N. asteroides and D. pneumoniae Type XIII. Progressive bronchopneumonia, despite massive suppressive chemotherapy directed against micro-organisms persistently sensitive in vitro, led to lobectomy. Operative specimen teemed with Nocardia. Postoperative empyema due to S. pyogenes var. aureus.

CASE 6.—A 38-year-old man with chronic lymphatic leukemia of four years' known duration had been well controlled on continuous cortisone therapy for 17 months, at which time he was admitted to the hospital solely for metabolic studies. Aside from mild chronic bronchitis, he appeared in good general condition. On the 11th day after a normal chest roentgenogram, and while afebrile, he complained of sharp pain in the left anterior thorax. A chest roentgenogram disclosed the interval appearance in the left upper lobe of a 3 cm. nodular lesion. His subsequent clinical course is charted in Figure 1.

The day following onset of pain he began to raise rusty sputum typical of that seen in pneumococcal pneumonia. Direct Gram stain showed many leukocytes, together with innumerable Gram-positive lanceolate diplococci. Type 13 Diplococcus pneumoniae (pneumococcus) was recovered in nearly pure culture. Penicillin therapy was begun, but, surprisingly, the lesion excavated within a few days and presented the appearance of an acute lung abscess.

Repeat Gram stain (Fig. 2*A*) of the sputum showed no identifiable D. pneumoniae but instead numerous Gram-positive branching actinomycete-like forms identified on culture as N. asteroides. The Nocardia was found to be highly sensitive in vitro to chlortetracycline. Reinspection of the initial sputum smear disclosed occasional similar branching forms, all but obscured by pneumococci (Fig. 2*B*). Chlortetracycline in high dosage was added to the regimen. Improvement was observed within a week with shrinking of the abscess cavity, more adequate drainage, and diminution of sputum production. To detect the branching forms of N. asteroides in Gram stain of the sputum became increasingly laborious and impossible by the end of two weeks' therapy. Four weeks after initiation of treatment, however, there was roentgenographic evidence of new infiltrations central to the original pulmonary lesion and reappearance of N. asteroides in smear and culture of pulmonary secretions. The pulmonary changes are illustrated by the serial chest roentgenograms (Fig. 3), which show the lesion two days after the onset of symptoms, the later inadequately drained tension cavity, and the progressive spread medially while on suppressive antibiotic chemotherapy. It was considered probable that the spread was bronchogenic, and it is possible that the employment earlier of aerosol enzymes to promote bronchial drainage may have contributed in an untoward manner.

A left upper lobectomy was performed. The specimen contained multiple pus-filled abscesses productive of pure N. asteroides on culture, and microscopically actinomycete-like forms were readily seen in tissue sections. His postoperative course was stormy because of an empyema due to coagulase-positive hemolytic S. pyogenes var. aureus. In time, this acute infection was controlled and the patient survived 18 months after lobectomy, at which time death occurred from leukemia and overwhelming staphylococcal sepsis. During the interval of more than a year the patient was observed upon many occasions and rehospitalized at intervals. Numerous materials were cultured frequently, including blood, sputum, and the draining cutaneous fistula, a remnant of the postoperative empyema. At no time after surgical extirpation of the left upper lobe was N. asteroides cultured from these specimens, nor was Nocardia asteroides

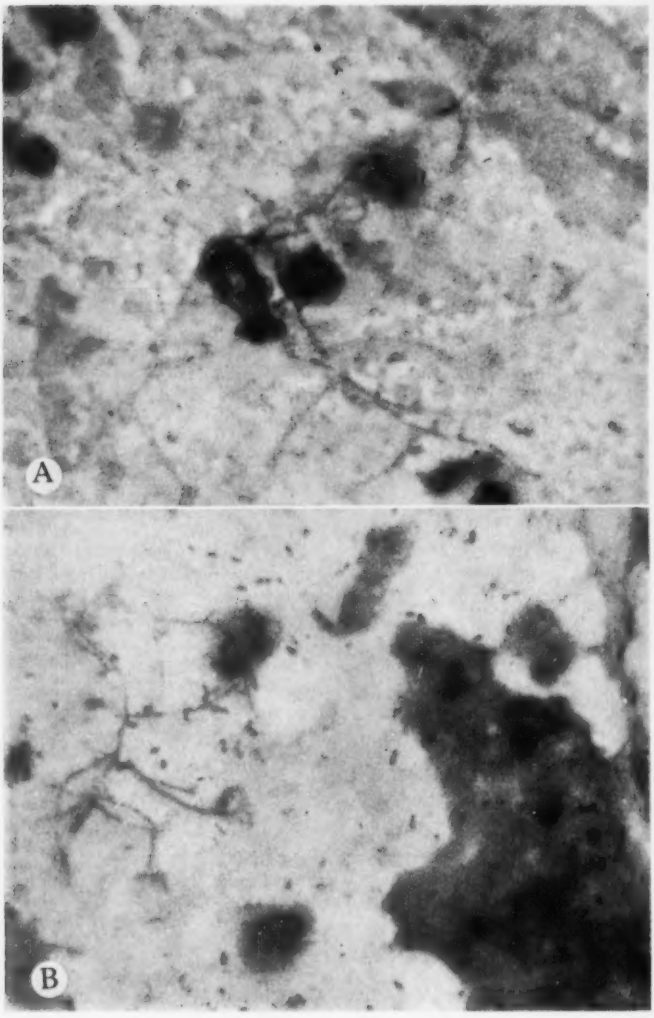


Fig. 2.—*A*, Gram stain of sputum in Case 6 after three days of penicillin therapy. Nocardia numerous, D. pneumoniae unidentifiable. *B*, Gram stain of sputum in Case 6 prior to penicillin therapy. Polymorphonuclear leukocytes, innumerable pneumococci, and occasional Nocardia are present.

Fig. 3.—Serial chest roentgenograms of Case 6. Left upper lobe pneumonitis and abscess due to D. pneumoniae, Type XIII, and to N. asteroides.

demonstrated by culture at autopsy, in tissue sections of any organs, or in the chronic empyema and associated soft-tissue abscesses.

Comment.—This is a remarkable instance of infection due jointly to Nocardia and D. pneumoniae. The clinical signs, a study of the stained sputum slides, and the appearance of the chest roentgenograms and of the operative specimen make it probable that the same area of lung was dually infected.

Despite the persistent sensitivity of the Nocardia to chlortetracycline in vitro, and the suppression of the organism from the sputum while the patient was being treated with this agent for a time prior to the spread medially, subsequent examination of the removed lung demonstrated the infection to be far from eradicated by the antimicrobial agent alone. This case represents cured nocardial infection, but by surgical extirpation of the lesion, not by antimicrobial therapy, at least as employed.

CASE 7.—A 36-year-old woman was treated at Memorial Center for generalized Hodgkins disease over a 13-year period. Antitumor therapy included sequentially radiation, triethylene melamine, cortisone, and finally prednisone. Adrenal corticosteroids were administered continuously for 35 months, but, with the development of a Cushing-like syndrome, she was admitted May 25, 1956, primarily to curtail these agents. This proved to be impossible; her course was highly stormy, and the admission became her last. It is outlined briefly here. Ref-

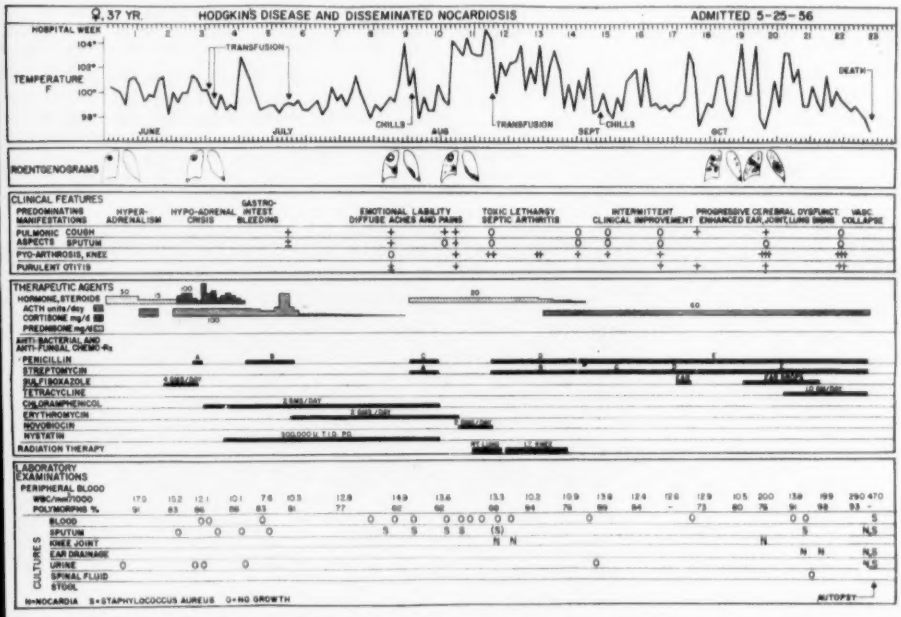


Fig. 4 (Case 7).—Hodgkin's disease associated with disseminated nocardiosis. For clarity, dosage regimens for penicillin and streptomycin are shown below. Capital letters refer to the superscripts over intervals of administration of these antibiotics shown in the Figure.

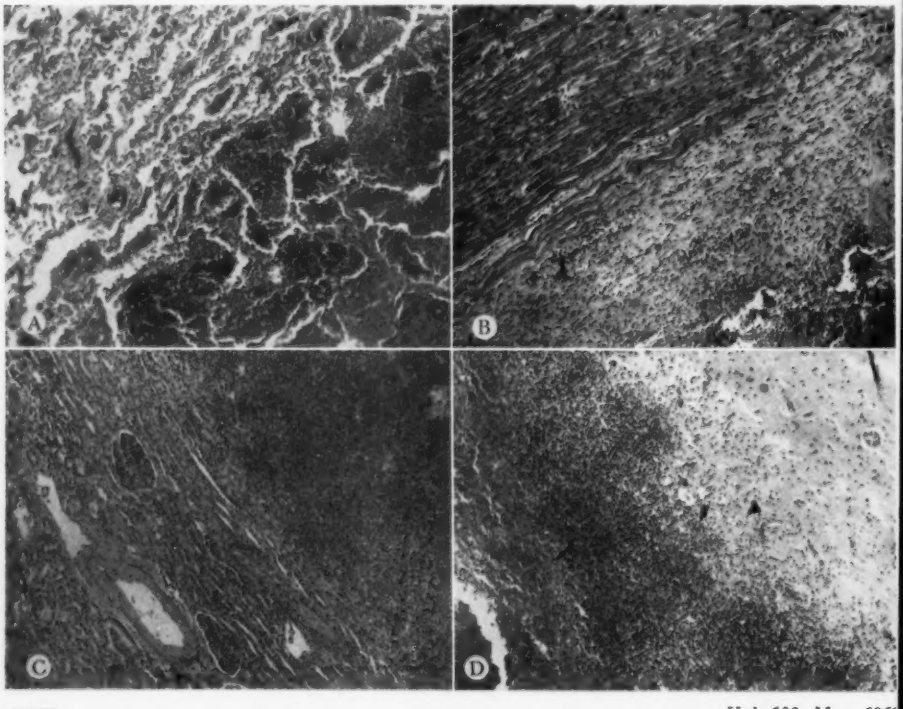
Drug	Interval	Dosage
Aq. penicillin G, units	A	400,000 q. 4h.
	B	400,000 q. 12h.
	C	300,000 q. 6h.
	D	1,000,000 q. 4h.
		+ probenecid (Benemid)
Procaine penicillin, units	E	600,000 q. d.
Streptomycin, gm.	A	0.5 q. 6h.
	B	1.0 q. 12h.
	C	1.0 q. d.
	D	0.5 q. d.
	E	1.0 q. d.

erence to Figure 4 will clarify the complexities through graphic illustration.

On admission she stated that intermittently for the preceding six months weakness, frontal headaches, blurring of vision, and low-grade fever had been present. Physical examination showed the stigmata of hyperadrenalism, mild generalized peripheral adenopathy, a barely palpable liver, and generalized muscular weakness. She had a moderate anemia and polymorphonuclear leukocytosis. Chest roentgenograms differed from those considered normal and taken nine months previously in showing a 4 cm. spherical density in the posterior segment of the right upper lobe. The nature of this lesion, whether infectious or neoplastic, was obscure. At no time was it possible to obtain a satisfactory specimen of sputum for culture.

Early in her hospitalization she developed adrenal insufficiency and severe gastrointestinal bleeding. After many trials of various regimens, she was stabilized and maintained on corticotropin (ACTH) intramuscularly, 60 units daily, which she received until her death. During June and July she continued to be febrile and anemic and leukocyte counts ranged from 10,000 to 18,000 per cubic millimeter. Many cultures from different sites, including multiple blood cultures, failed to elucidate the problem. In August came the clue. A knee joint became acutely inflamed, and yellow pus was obtained by aspiration. The fluid yielded N. asteroides in pure culture. Her condition thereafter deteriorated rapidly. Temperature elevations to 104 F were frequent; she was lethargic and anorectic. Additional patchy areas of bilateral pulmonary parenchymal involvement were noted on chest roentgenograms, together with increased markings from the hilum toward the lung abscess. It was considered probable that the pulmonary lesion was also due to Nocardia, but this was not definitely shown until autopsy. Because the possibility existed that the lung lesion was neoplastic, roentgen therapy was directed to the right upper lobe. The results were equivocal. Antibiotics in massive dosage, both systemically and intra-articularly, failed to alter her course.

Fig. 5*A* (Case 7), lung. Abscess due to N. asteroides, consisting of necrotic debris and fibrin centrally, with a peripheral collection of inflamatory cells. Fibrous encapsulation is lacking. The Nocardia are readily visualized in suitably stained sections observed with higher magnification. Hematoxylin and eosin; ×125. *B* (Case 7), papillary muscle, left ventricle of heart. An abscess is present composed of degenerating muscle fibers, connective tissue, and leukocytes, together with numerous branching Nocardia. Hematoxylin and eosin; ×125. *C* (Case 7), renal cortex. The abscesses are due to N. asteroides. Hematoxylin and eosin; ×125. *D* (Case 7), mycotic abscesses in brain. Hematoxylin and eosin; ×125.



She received variously penicillin, streptomycin, sulfisoxazole, chloramphenicol, erythromycin, novobiocin, and nystatin without evidence of response in the lung lesion, which instead enlarged somewhat and manifested cavitation, or in the sites of systemic spread. The roentgenographic appearance of the cavity and lung field bore striking resemblance to that in Case 6.

Mental changes were in evidence, varying from profound lethargy to cheerful excitement. Headaches became severe, and a persistent earache culminated in October in a frank otitis media and externa. Culture of the purulent ear drainage was positive for Nocardia. Blood cultures remained sterile. Cultures of spinal fluid were sterile. The patient gradually lapsed into coma and died Nov. 1, 1956.

At autopsy there was widespread tumor involvement of the peritoneal surfaces, spleen, adrenals, stomach, lymph nodes, brain, and bone marrow. There was a perforating peptic ulcer on the greater curvature of the stomach. Numerous small abscesses containing greenish-yellow pus due to N. asteroides were found in the papillary muscle of the mitral valve leaflet, the parenchyma of the liver, pancreas, subcortical areas of both kidneys, the thyroid, and the cerebral cortex. In the lungs, there were numerous nodules with central necrosis, due to Nocardia, up to 3.5 cm. diameter.

Microscopic examination of both lungs showed circumscribed areas of necrosis, leukocytic infiltration, and fibrinous exudation around the periphery (Fig. 5*A*). Branching forms of N. asteroides were identified in all areas. The papillary muscle showed degenerating muscle fibers and connective tissue with acute purulent inflammation in the wall around the abscess (Fig. 5*B*), together with beaded branching filaments compatible with Nocardia. Similar lesions containing organisms resembling Nocardia were found in the liver, pancreas, kidneys (Fig. 5*C*), cerebrum (Fig. 5*D*), and cerebellum. Cultures obtained from the right temporal bone, pancreas, brain, kidney, lung, and liver were all positive for N. asteroides.

Comment.—This case represents classical metastatic infection, as well as the usual fatal outcome of patients with central nervous system involvement.[8] Although the organisms were clearly being seeded to widespread bodily sites, numerous blood cultures failed to demonstrate this fact.

Pulmonary involvement by Nocardia is the most frequent site of disease.[9] Even so, in this case as in Case 6, the lung pathology was a problem in differential diagnosis, for Hodgkin's disease (and leukemia) could have presented similar lessions.[10,11]

The pathologic descriptions, as well as the photomicrograph, are representative of the gross and microscopic pathologic findings in nocardial infection. The characteristic lesions are small abscesses composed of a center of necrotic material and fibrin, with some polymorphonuclear leukocytes, lymphocytes, and plasma cells in the adjacent tissue and with branching mycelia (observed only with appropriate staining) scattered throughout the area. Occasionally, there is a very scant wall of fibrous tissue.

It is noteworthy that the strain of Nocardia isolated in this case was susceptible in vitro to several of the antimicrobial agents used, despite which there was spread of the pulmonary lesions and development of the knee infection during therapy with one of them, erythromycin; nor did the other agents employed in both customary and massive doses have demonstrable benefit.

Characterization of Strains of Nocardia Recovered, Including Tests in Vitro of Sensitivity to Antibiotics

On initial isolation, all strains displayed the accepted characteristics of N. asteroides, as set forth in "Bergey's Manual of Determinative Bacteriology" [12] and Schneidau and Shaffer.[13] Surface growth was rapid on routine blood agar or starch agar mediums under aerobic conditions at 37 C. The color of young cultures was yellowish-white to cream, which darkened after prolonged growth to shades as deep as coral. Filamentous hyphae, Gram-positive and partially acid-fast and possessing the characteristic branching and tendency to fragmentation, were observed in stained smear.

At the time of review of this material, at least one strain of Nocardia was still available from each case, having been maintained by periodic subculturing. After transplantation to obtain fresh growth, it was found after 10 days' incubation that no strain had hydrolyzed casein, one strain liquefied gelatin, and all but two were urease-negative. The latter two were urease-positive within 48 hours.

TABLE 2.—*Characteristics of Seven Strains of Nocardia Asteroides Isolated from the Cases Described*

Case	Source of Strain	Antibiotics Used in Recent Past Prior to Date of Isolation	Biochemical Behavior			Minimal Inhibiting Concentrations, γ/Ml. for Complete Inhibition (Incubation Period 48 Hr. at 37 C)									
			Gelatin Liquefaction	Casein Hydrolysis	Urease	Penicillin	Streptomycin	Chlortetracycline	Oxytetracycline	Chloramphenicol	Erythromycin	Novobiocin	Neomycin	Polymyxin	Bacitracin
1	Breast abscess	Tetracycline, 2 gm. per day ×4 wk.; procaine penicillin (several injections)	—	—	+	0.4	50	25	12	12	20	>200	<2	>100	—
2	Sputum	Penicillin, amount unknown, 5 mo. before	+ (10 days)	—	—	>6	3	100	100	6	1.2	25	8	>100	—
3	Lung, autopsy	Chloramphenicol, 1 gm/day ×8 wk.; tetracycline 1 gm/day ×1 wk.	—	—	+	>6	>100	50	50	25	>20	100	16	>100	—
4	Blood culture	Intermittent "prophylactic" penicillin and tetracycline throughout 2 yr. period	—	—	—	>6	12	100	100	25	0.6	25	4	>100	—
5	Brain abscess	None	—	—	+	>6	100	25	50	25	>20	200	1.2	>100	50
6	Sputum	Uncertain; possibly chlortetracycline & penicillin in large amounts	—	—	—	>6	6	100	100	50	1.2	25	8	>100	—
7	Knee joint, initial isolate	Penicillin, 21,000,000 units/19 days; streptomycin 2 gm/day ×7 days; chloramphenicol 2 gm/day ×6 wk.; erythromycin, 2 gm/day ×4 wk.	—	—	—	>6	6	>100	>100	12	0.6	25	4	>100	—

Tests in vitro, with use of commercial medicated disks, of sensitivity to various antibiotics were done at the time the stains were originally isolated. With use of this relatively crude assessment, increased resistance to a given antibiotic could be discerned in some instances when patients were treated with that antibiotic, provided sequential isolates of Nocardia were obtained over a period of time; e.g., the strains of Nocardia isolated in Case 7 prior to the employment of streptomycin were partially sensitive to that agent, whereas strains isolated at postmortem examination after prolonged use of streptomycin were resistant. An inconsistency appears in that the strains isolated five years ago from the sputum of Case 6 during a course of intensive chlortetracycline therapy remained sensitive throughout, although isolation of the later strains did occur during clinical relapse while the patient was on therapy. When retested five years later by more accurate techniques they are presently found to be chlortetracycline-resistant. Whether mutations following repeated subculturing have occurred or whether the disks employed originally were not standardized properly is unknown.

Unfortunately, not all strains were saved, but representative isolates from each case have been. Some of these have been transplanted repeatedly, but it seems improbable that this has affected greatly the data presented in Table 2, wherein the results of testing simultaneously all the available strains for sensitivity, with use of a plate dilution method with twofold dilutions of antibiotics, are shown. The media for testing was comprised of 1.5% agar, fresh heart infusion broth, Bacto-Peptone, 1.5% NaCl, with a pH adjustment to 7.2-7.4.

To perform the tests, a swab was used to remove the surface growth of Nocardia on a blood agar plate after 48 hours' incubation. This was suspended in tryptone water, then reswabbed over the surfaces of a series of plates which contained serial dilutions of antibiotics. Incubation was carried out at 37 C. Observations were recorded of both complete and partial inhibition at the end of 48 hours, 72 hours, and 96 hours. The end-point for complete inhibition was taken as the lowest final concentration of antibiotic on which there was no discernible growth after 48 hours. The end-point for partial inhibition was considered to be the lowest concentration, either on which growth was not discerned until 48 hours or on which there was much less growth as compared with the growth of the same strain on antibiotic-free agar.

Values for complete inhibition after 48 hours' incubation are shown in Table 2 along with an indication of the chemotherapy employed during a seemingly relevant interval of time prior to isolation of the strain.

The most striking feature is the marked natural variability in sensitivity to various antibiotics, particularly to streptomycin, erythromycin, and novobiocin, but this variability was also observed, at times in sport-like manner, to the other antibiotics. To illustrate this, the strain from Case 1 is markedly more sensitive to penicillin and neomycin than any of the remaining strains, while at the same time it is much more resistant to erythromycin and novobiocin than most other strains. Such strain variations could not be correlated in any convincing manner with morphologic or biochemical differences, with previous antibiotic exposure, or with the clinical course. No concurrent study was undertaken of the virulence in animals of these strains, although Runyon has advocated this.[14]

The effect of duration of incubation, 48 hours as against 96 hours, while not shown in the Table, was akin to that often observed in tests of bacterial sensitivity, i. e., the concentration of antibiotic required for complete inhibition was raised during the longer interval of incubation by one- or even twofold. Even so, at 96 hours, four of seven strains were completely inhibited by less than 25μg. of chloramphenicol per milliliter, 2.5μg. of erythromycin per milliliter, and 50μg. of novobiocin per milliliter, levels

which may still lie within therapeutically obtainable serum concentrations.

The end-point of partial inhibition was observed in most instances in the next lower dilution of antibiotic, but variations up to fourfold were noted.

Comment

The case reports, and, more especially, the illustrative comment following each one, serve as the basis for the discussion. For brevity this material will not be reiterated here. We have preferred to discuss, in the comments, pertinent features at a point in the text where attention upon them could best be focused.

The introduction to this paper alluded to an apparent rarity of nocardiosis, yet our seven cases were detected in five years. Moreover, during that interval the genus Nocardia was isolated from perhaps a dozen additional patients, usually from the routine cultures of the nose, and occasionally the throat, of pediatric admissions. These latter strains were not saved or considered in this report, since at the time they appeared to have no clinical significance. These findings emphasize, however, our opinion that watchfulness, allied with careful laboratory performance, will disclose many unsuspected cases of nocardiosis and support the more recent contentions, increasingly convincing, that diseases due to the deep mycoses are much commoner than formerly supposed.

The types of disease which this hospital undertakes to treat may bear significantly upon the frequency of cases. Patients with lymphomas and leukemias are generally believed to be susceptible to infection. In them, decreased antibody response and generalized deficiency in the immunologic mechanism have been described.[15,16] So too, antineoplastic therapy, notably the long-term use of corticotropin or adrenal corticosteroids, may affect variously both immunologic and inflammatory responses and perhaps even promote dissemination of the invading parasite.

Diagnosis is especially apt to be delayed in patients who have such neoplastic diseases as leukemia or Hodgkin's disease in whom fever, abnormal hematologic findings, and other signs or symptoms may be attributable to neoplasm or be masked by antineoplastic therapy. In them awareness may be blunted and infection as a factor underestimated.

With regard to antimicrobial therapy, an unsatisfactory correlation was noted between apparent sensitivity in vitro to an antimicrobial agent and the clinical response attending its use. While this may reflect the type of host, the same experience has been recorded by others.

In retrospect we believe that more consideration should have been given to intensive sulfonamide therapy in these cases. Although sulfonamides appear inferior to broad-spectrum antibiotics on the basis of in vitro tests, the clinical response of patients under treatment with these agents, as well as studies of their protective effect in animals infected experimentally, suggest strongly that they are superior in vivo. In a recent review summarizing the experience of many, Procknow and Loosli [17] recommend sulfonamides combined with an effective broad-spectrum antibiotic. They concur with us that surgical measures must be considered. Three of our patients were cured of nocardiosis with surgical extirpation of the focus. It is important to note that amphotericin B is completely ineffective against Nocardia species, at least when tested in vitro.

The data on sensitivities are included chiefly to point out the possible value of such tests in the detection of microbiologic variations between strains of Nocardia which may not be apparent if the customary and accepted procedures of determinative microbiology alone are employed in the differential identification.

Summary

Seven cases of infection due to Nocardia asteroides are presented. In five there was coexisting neoplastic disease. In this group of cases of nocardiosis, cure in three instances was associated with surgical extirpation of the infectious lesion. Death was

considered due primarily to nocardiosis in two of the cases, to cancer in two others.

The detection of nocardiosis in the cases with cancer was frequently difficult, and the pathogenesis of the infection obscure. This is attributed in some instances to the presence of neoplastic disease, in others possibly to the use of long-term therapy with corticotropin (ACTH), cortisone, or prednisone and its attendant alterations in host response.

No recommendation as to antimicrobial therapy of choice can be made on the basis of the cases described. Antibiotic therapy alone was not conspicuously successful in eradicating the infection, despite hopeful expectations based on tests in vitro of sensitivity. Suppression of the infection was achieved in several instances. The accumulated literature now suggests the sulfonamides might have proved more effective and should have been used.

Tests for sensitivity to various antibiotics in vitro of the strains of Nocardia isolated from these seven cases suggest that variations in strains not discerned by the standard procedures of determinative bacteriology may be detected by this means.

Miss Anne H. Blevins, technician-in-chief of the diagnostic Bacteriology Laboratories, Memorial Center provided technical assistance. Mrs. Tefta Zografi Iralu and Miss Eleanor Benter assisted in some of the microbiologic studies.

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Carbohydrate Metabolism in Brain Disease

XI. Effects of Thioctic (Alpha-Lipoic) Acid in Chronic Schizophrenia

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Earlier studies made at this laboratory showed that the injection of glutathione improved the abnormal metabolism of keto acids that occurs in psychoses and also improved the clinical status of patients with manic-depressive or schizophrenic psychoses.[1] It was considered desirable to study further this apparent relation between clinical condition and state of keto acid metabolism. Earlier work had shown that giving thiamine, a vitamin essential to the oxidation of keto acids, did not ameliorate the chronic psychoses under consideration here, and hence it was decided (at the suggestion of Dr. W. W. Westerfeld) to study the action of thioctic acid, the other vitamin concerned in the utilization of the keto acids. An additional reason for studying thioctic acid concerned its sulphur content: Some sulfur-containing compounds inactivate sympathomimetic amines, as shown by Schroeder et al.,[2] and there is reason to suspect that some symptoms of the psychoses studied in these experiments may be due to overproduction of epinephrine or of related substances.[3]

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From the Laboratory of Clinical Physiology, McLean Hospital.

Material and Methods

Six schizophrenic women, aged 25 to 48, were studied. The methods used were as previously described.[4]

Observations

CASE 1.—A 48-year-old woman was hallucinated and deluded. The patient showed great tension when she was troubled by her hallucinations, but at other times she was sociable and good-natured, though silly. When thioctic acid was given intramuscularly for 45 days in daily doses of 20 mg. and then for 15 days in daily doses of 40 mg. she showed moderate relaxation of tension but there was no change in the abnormal carbohydate metabolism. Raising the dose to 200 mg. a day caused no clinical change for the first two weeks, but in the third week the patient became progressively more apathetic, hallucinated, and worried-looking. Her usual sociability disappeared, and she sat about listlessly. Studies made at this time showed further impairment of the utilization of pyruvate and lactate and the appearance of an abnormal curve of α-ketoglutaric acid utilization; the curves of glucose and citrate utilization were not changed (Fig. 1). Ten days after discontinuation of the

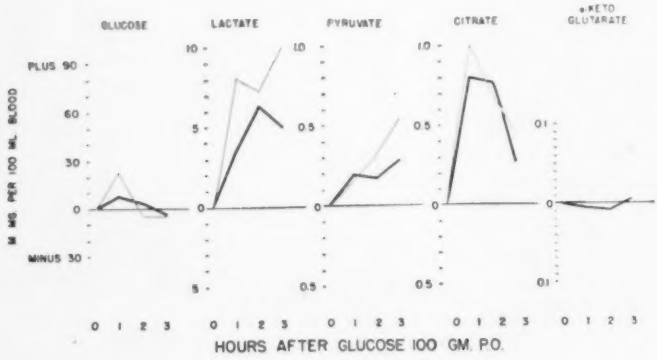

Fig. 1.—Findings in Case 1. Solid lines indicate values before thioctic acid was given; dotted lines indicate values during its administration.

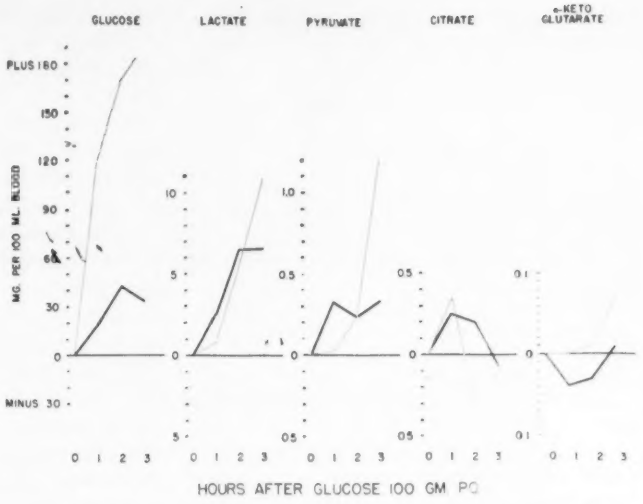

Fig. 2.—Findings in Case 2. Solid lines indicate values before thioctic acid was given; dotted lines indicate values during its administration.

thioctic acid, the patient's symptoms had reverted to their earlier degree of abnormality.

CASE 2.—A 25-year-old woman was deluded, seclusive, and anorectic. Most of the patient's food intake consisted of candy. She was polite but vague when spoken to; however, she was neat and clean. Thioctic acid, in doses of 20 mg., was given daily for four weeks. No change was observed during the first three weeks, but thereafter the patient became markedly withdrawn, huddling against the wall and preferring a room with shades drawn. She was disheveled and seemed confused and worried. Studies made at this time showed worsening of the curves of utilization of glucose, lactate, pyruvate, and α-ketoglutarate. The curve of citrate utilization was unchanged (Fig. 2).

CASES 3 and 4.—Two women aged 25 and 38 were paranoid, deluded, and recurrently hallucinated. The first was given thioctic acid in daily intramuscular doses of 40 mg.; she became clinically worse in two weeks, and hence the thioctic acid was discontinued. No studies of carbohydrate metabolism could be made, since the patient was too ill to cooperate. The other patient received 40 mg. a day intramuscularly for a month and then 100 mg. a day, also for a month. The smaller dose caused no change; the larger dose made the patient so much more aggressively paranoid that studies could not be made.

CASE 5.—A 38-year-old woman was markedly anxious and deluded. The patient dressed carelessly and was generally indifferent to her surroundings. After receiving 100 mg. of thioctic acid daily by mouth for two months, she was less tense and anxious and more cooperative. Studies made at this time (Fig. 3) showed improvement in all the curves of utilization of carbohydrate intermediates. The dosage was then increased to 100 mg. by

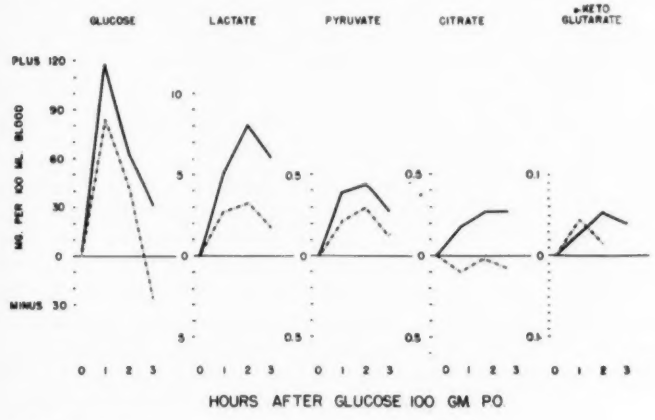

Fig. 3.—Findings in Case 4 while receiving 100 mg. thioctic acid. Solid lines indicate values before thioctic acid was given; dash-dot lines indicate values during its administration.

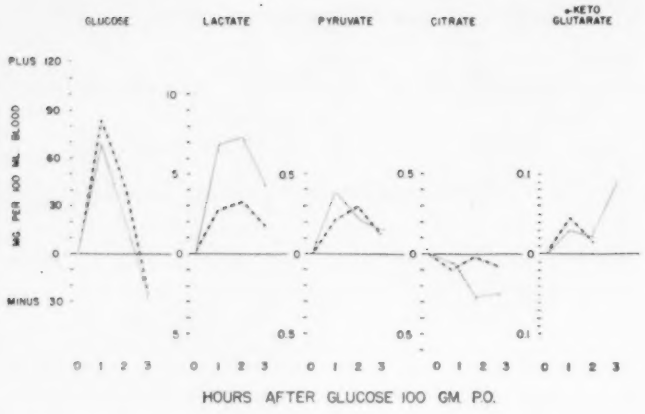

Fig. 4. — Findings in Case 4 while receiving 100 and 200 mg. thioctic acid. Dash-dot lines indicate values while receiving 100 mg. daily, and dotted lines while receiving 200 mg. daily.

mouth twice daily, and in seven weeks the patient became noticeably more irritable and anxious. Studies made at this time (Fig. 4) showed worsening of the curves of utilization of lactate and α-ketoglutarate and perhaps of pyruvate. The curves of glucose and citrate were not worsened. Giving thiamine, 250 mg. a day by injection, for 10 days caused no change in the patient's clinical or biochemical status. She returned to her approximately original clinical condition about 10 days after the thioctic acid was discontinued.

CASE 6.—A 30-year-old woman was deluded, depressed, and markedly fearful and anxious. In the past she had had hallucinations. Giving thioctic acid, 100 mg. by mouth, for a month caused considerable lessening of the anxiety and tension, but no significant change in biochemical status was observed.

Comment

The effects of thioctic acid cannot yet be defined, since there is no extensive body of knowledge about its physiologic role and pharmacologic actions in mammals. On the one hand, administering the vitamin caused lessening of tension in three of the six patients who received it. This change might have been a placebo effect, even though it occurred in patients who had received other substances by mouth or by injection without showing such an effect. If the change was a genuine pharmacologic effect, its mechanism is unknown at present: however, one patient who improved clinically exhibited a concomitant improvement in keto acid metabolism.

On the other hand, administration of similar doses of the vitamin to three other patients caused worsening of the schizophrenic manifestations, and in two of the three patients who had apparently improved on small doses, large doses caused exacerbation of the illness. The mechanism underlying this effect is not evident, although one possibility suggests itself: namely, that the excess of thioctic acid administered caused thiamine deficiency. Thioctic acid is the co-factor of thiamine in the oxidation of keto acids, and nutritional practice affords many instances of the inadvertent production of a vitamin deficiency by giving a great excess of another vitamin that is involved in the same metabolic process. The idea that large doses of thioctic acid cause thiamine deficiency is supported by the findings of the present study, which showed that such doses caused deterioration of keto acid metabolism. It is of interest that Horwitt[5] found some years ago that inducing thiamine deficiency in schizophrenic patients aggravated their disease.

Whatever the mechanism of the deterioration in keto acid metabolism that was observed in the present study, the metabolic change itself is worthy of note because it was accompanied by clinical worsening. In an earlier study made at this hospital improvement in keto acid utilization was accompanied by amelioration of mental symptoms—in schizophrenia when gluta-

thione was administered [1] and in Wernicke's syndrome when thiamine was given.[6] All these data support the idea that mental function may be greatly influenced by the state of keto acid utilization. This seems to be true in other diseases as well: For example, patients with Cushing's syndrome exhibit defective keto acid utilization [7] and also show mental symptoms. Similarly, Sherlock and co-workers [8] and Strohmeyer et al.[9] found that deterioration in the mental state, i. e., disorientation progressing to coma, occurred in patients with cirrhosis when utilization of keto acids became highly abnormal. On the other hand, the utilization of keto acids may be impaired in some patients with multiple sclerosis in whom mental state is normal,[10] although of course mental changes may occur in this syndrome also. It seems, therefore, that very marked impairment of keto acid utilization, as in severe hepatic disease, may by itself cause mental deterioration, whereas in the other conditions listed above it plays only a contributory and peripheral role.

At any rate, the findings of the present study, as well as the other data discussed above, strongly suggest that factors that impair keto acid utilization aggravate mental symptoms in many diseases, including schizophrenia.

Summary and Conclusions

Thioctic (α-lipoic) acid was given to six chronically schizophrenic patients. Three showed slight improvement on small doses; five of the six showed considerable worsening on large doses. Impairment of keto acid utilization accompanied clinical worsening. The mechanism underlying the biochemical change is not known; it is possible that excessive intake of thioctic acid precipitated thiamine deficiency. The data of this and other studies suggest that impairment of keto acid utilization causes mental disturbances.

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Carbohydrate Metabolism in Brain Disease

XII. Effects of Epinephrine on Intermediary Carbohydrate Metabolism in Normal and Schizophrenic Subjects

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Abnormalities in carbohydrate metabolism that occur in patients with schizophrenic, manic-depressive, and involutional psychoses have been described in earlier communications from this laboratory.[1-4] In psychotic subjects the administration of glucose is frequently followed by excessive or prolonged elevations of blood levels of glucose, lactate, pyruvate, citrate, and α-ketoglutarate in psychotic subjects. However, these abnormalities are not specific, since they occur in various other diseases.

Since there is evidence that there is increased secretion of both cortical and medullary hormones of the adrenal glands in mental disorders,[5] it seemed likely that some of the abnormalities of carbohydrate metabolism of psychotic patients might be caused or at least modified by the action of these substances. Earlier work, done at this hospital,[3] showed that hydrocortisone caused elevations of blood levels of glucose, lactate, and pyruvate after administration of glucose greater than those found in the same subjects not under the influence of hydrocortisone. Likewise, parenteral injection of epinephrine given without glucose was shown to cause increases in the values of all five carbohydrate moieties studied.[6] The purpose of the present project was to ascertain to what extent epinephrine increased these values in subjects given glucose.

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Methods and Materials

Six control subjects and six psychotic patients were studied. The control group, all of whom were volunteers, comprised hospital employees and members of the nursing staff at McLean Hospital. The patients were all hospitalized for either schizophrenic or schizoaffective disorders. The ages of the control group ranged from 20 to 34 years, whereas those of the patients were from 25 to 49. There was not illness, other than psychiatric, in the subjects. All were well nourished and were eating well.

The experiments consisted of the oral administration of 100 gm. of glucose to each subject on two occasions. Epinephrine was given intravenously throughout one of the tests; the other test served as a control. All subjects were in the fasting state and had rested at least one-half hour before the commencement of the test. Complete bed rest was maintained by all subjects throughout the three-hour period following the ingestion of glucose.

The epinephrine solution was composed of 400μg. of epinephrine chloride solution (1:1,000, Parke-Davis) in 500 ml. of isotonic sodium chloride solution. An infusion of this mixture was started immediately after blood for fasting determinations had been drawn, and a few minutes later glucose was administered. The speed of the epinephrine infusion was adjusted so that the total 500 ml. might be delivered during the three hours of the test, provided that pulse and blood pressure remained substantially unaltered; if elevation of these values occurred, the rate of the drip was slowed. In most cases it was possible to administer the entire 500 ml.; every subject received more than 400 ml. An additional experiment consisted of the infusion of epinephrine in four subjects, who fasted during the entire procedure; three of them were also subjects in the previously described experiments with glucose.

Blood was drawn for estimations of concentrations of glucose, lactate, pyruvate, α-ketoglutarate, and citrate before and at one, two, and three hours after ingestion of glucose; the methods used have been described in detail elsewhere.[1] In addition, fasting and three-hour levels of blood eosinophils[7]

and reduced glutathione[8] were measured in most subjects.

Statistical comparison of the curves obtained with and without epinephrine was made by means of a "split plot" analysis of variance.[9] Data were analyzed for the influence of time, epinephrine, diagnostic category (psychotic patients vs. control subjects), and individual variability; interactions of these factors also were computed. No statistical analysis was done in tests where only epinephrine was given. The effect of epinephrine on blood eosinophil and reduced glutathione values was evaluated by subjecting the mean differences observed for zero and three hours to tests for "paired data."[10]

Data are summarized in Table 1 which shows mean hourly change from fasting values for each substance both with and without epinephrine; control subjects and patients were treated together. These results, subdivided further to illustrate differences between control and psychotic groups, appear graphically in Fig. 1.

TABLE 1.—*Average Hourly Changes of Carbohydrate Moieties from Fasting Levels Following Oral Glucose Administration With and Without Epinephrine* *

	Hr.	With Epinephrine	Without Epinephrine	Difference Between Means	Standard Error of Difference Between Means †
Glucose	1	106.0	40.8	65.2 ‡	
	2	77.8	15.4	62.4 ‡	±10.1
	3	48.2	−1.8	50.0 ‡	
Lactate	1	7.42	4.63	2.79 ‡	
	2	9.36	3.51	5.85 ‡	±0.96
	3	7.20	2.51	4.69 ‡	
Pyruvate	1	0.460	0.217	0.143 ‡	
	2	0.400	0.151	0.249 ‡	±0.065
	3	0.236	0.064	0.172 ‡	
Citrate	1	0.271	0.249	0.022	
	2	0.043	0.051	−0.008	±0.088
	3	0.198	−0.151	−0.047	
α-Ketoglutarate	1	0.0256	0.0009	0.0247	
	2	0.0264	0	0.0264	±0.0128
	3	0.0355	0.0073	0.0282 ‡	

* Values in mg/100 ml.
† Reference 9, Chapter 7.
‡ Differences significant at $P=0.05$.

Observations

Changes in Carbohydrate Fragments.—The importance of the passage of time on blood levels was established in all metabolites except α-ketoglutarate; this was highly significant ($P<0.01$)* for the glucose, pyruvate, and citrate changes, and significant ($P<0.05$) for the lactate changes. Since such an influence would be expected from the fact that the orally administered glucose is being metabolized during the course of three hours, no further comment will be made on this point.

1. Blood Glucose: The effect of epinephrine was highly significant. Blood glucose levels averaged 65.2, 62.4, and 50.0 mg. per 100 ml. blood higher at one, two, and three hours, respectively, when epinephrine was

* As used henceforth in the discussion of data, the terms "significant" and "highly significant" will have these meanings.

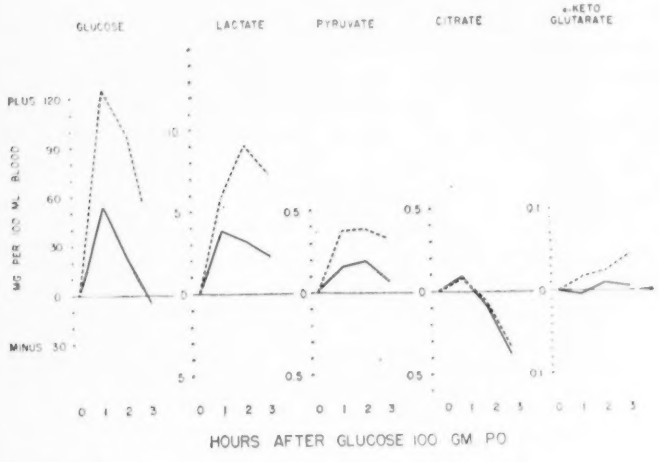

Fig. 1A.—Changes in carbohydrate moieties following oral administration of 100 gm. of glucose with and without epinephrine in control subjects. Solid lines indicate values without and broken lines with epinephrine.

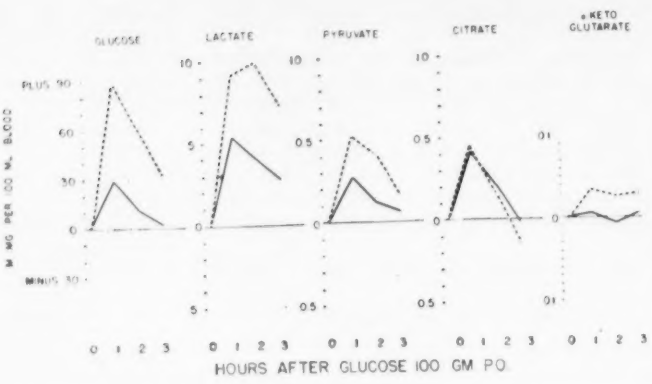

Fig. 1B.—Changes in carbohydrate moieties following oral administration of 100 gm. of glucose with and without epinephrine in psychotic subjects. Solid lines indicate values without and broken lines with epinephrine.

administered (Table 1). In addition, there was a significant difference between the over-all reaction of psychotic patients and control subjects; both with and without epinephrine blood sugar levels for the patients showed lower means (Fig. 1).

2. Blood Lactate: The effect of epinephrine was highly significant. Mean blood lactate elevations above fasting values were 7.42, 9.36, and 7.20 mg. per 100 ml. blood at one, two, and three hours, respectively, when epinephrine was administered; when glucose alone was given, the comparable values were 4.63, 3.51, and 2.51 mg. per 100 ml. of blood (Table 1). The amount of change in psychotic patients was not significantly different from that found in the normal subjects (Fig. 1).

3. Blood Pyruvate: The effect of epinephrine was highly significant. Mean blood pyruvate elevation above fasting values were 0.460, 0.400 and 0.236 mg. per 100 ml. blood at one, two, and three hours, respectively, when epinephrine was given; with glucose alone, comparable values were 0.217, 0.151, and 0.064 mg. (Table 1). A statistically significant difference in the shapes of the pyruvate curves of the psychotic and control groups also was apparent. In the control group, pyruvate values continued to rise until the second hour, both with and without epinephrine; in the patient group, however, maximal values occurred at the first hour in both tests (Fig. 1).

4. Plasma Citrate: The infusion of epinephrine had no significant influence on plasma citrate levels when glucose was given (Table 1). However, a significant difference between psychotic and control subjects in the citrate curve was apparent; levels of this substance at each hour were higher in psychotic patients whether or not epinephrine was used (Fig. 1).

5. Blood α-Ketoglutarate: The effect of epinephrine was significant, but not highly so. Average changes from fasting levels were 0.0256, 0.0264, and 0.0355 mg. per 100 ml. of blood at one, two, and three

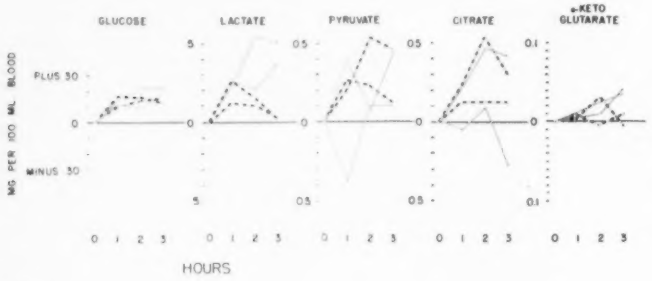

Fig. 2.—Changes in carbohydrate moieties in two control and in two psychotic subjects during infusion of epinephrine alone. Dotted lines indicate findings in normal subjects.

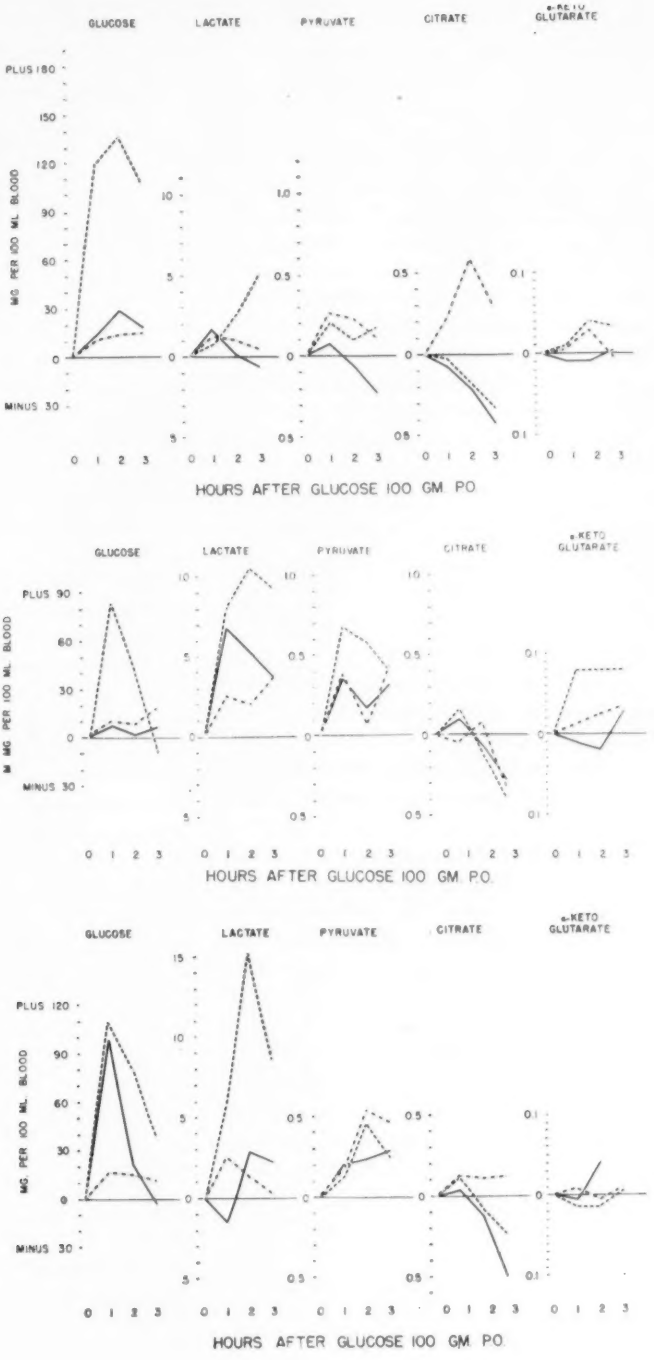

Fig. 3.—Comparison of changes in carbohydrate moieties in three patients during tests with glucose (solid line), with epinephrine (dash-dot line), and with (glucose and epinephrine (broken line).

TABLE 2.—*Average Fasting and Three-Hour Values of Eosinophils and of Glutathione Concentration Following Oral Glucose Administration With and Without Epinephrine*

		Fasting Level	3-Hr. Level	Difference	Standard Error of Difference	*t*	*P*
Eosinophil/cu. mm.							
With epinephrine	(14 subjects)	213.1	191.9	21.3	±5.52	3.86	<0.005
Without epinephrine	(10 subjects)	219.4	197.7	21.7	−5.48	3.96	<0.005
Glutathione/100 ml.							
With epinephrine	(14 subjects)	38.9	41.8	3.0	0.680	4.37	<0.001
Without epinephrine	(10 subjects)	39.3	39.9	0.6	0.712	0.843	

hours, respectively, when epinephrine was employed; comparable values when glucose only was given were 0.0009, 0, and 0.0073 mg. (Table 1). No other statistically significant results were obtained (Fig. 1).

Influence of Epinephrine Given Alone.—Epinephrine was administered intravenously in four subjects who received no glucose on that occasion (Fig. 2). Average values of all five carbohydrate moieties were raised by this infusion. Three of these subjects also received oral glucose with and without epinephrine as described previously (Fig. 3). It is apparent by inspection that the influence of intravenous epinephrine administered during a glucose tolerance test is not regularly accounted for by the algebraic summation of the effects of glucose and epinephrine individually.

Blood Reduced Glutathione and Eosinophil Counts.—The concentration of reduced glutathione per 100 ml. of erythrocytes was significantly increased when epinephrine was given (Table 2). Fasting average values were 38.9 and 39.3 with and without epinephrine, respectively, while corresponding three-hour values were 41.8 and 39.9. Eosinophil average values per cubic millimeter decreased in a statistically significant manner in experiments, both with and without epinephrine. Fasting mean levels were 213.1 and 219.4, with and without epinephrine respectively, while comparable three-hour values were 191.9 and 197.7. Epinephrine had no statistically important effect when average changes in eosinophils were compared.

Comment

The effect of intravenous administration of epinephrine on the metabolism of ingested glucose is established by the data presented here. With exception of blood citrate the concentration of all carbohydrate fragments measured after the ingestion of glucose showed significant or highly significant elevations when values obtained with epinephrine were compared with values obtained without it.

These results are not surprising. Elevation of blood glucose, lactate, and pyruvate after injection of epinephrine alone, and also during glucose administration alone, have been consistently reported [6,11-13]; it was to be expected that levels of these substances would be much higher when two influences with a similar effect were introduced simultaneously. Similarly, since epinephrine alone has been shown to raise the α-ketoglutarate level,[6] epinephrine might be expected to increase in concentration of this substance during glucose administration. The metabolism of the two keto acids, i. e., pyruvic and α-ketoglutaric, is similar in that phosphopyridine nucleotide, thiamine, thioctic acid, and coenzyme A are all required for the oxidation of both [11]; it is reasonable to assume that epinephrine affects both keto acids in the same manner.

The plasma citrate levels present a more complex problem. No effect of epinephrine on the citrate curve after administration of glucose was observed; however, when epinephrine was injected in patients not given glucose a rise in values occurred (Fig. 4). There is usually a fall in this substance

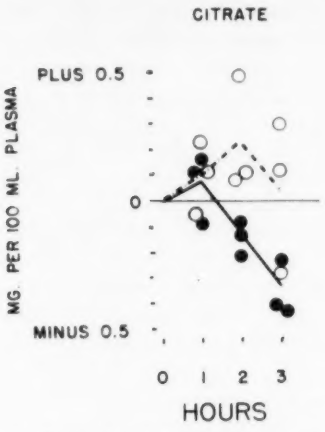

Fig. 4.—Comparison of changes in plasma citric acid levels with epinephrine alone and with glucose and epinephrine together. Open circle indicates epinephrine alone. Solid circles indicate epinephrine and glucose. Dash-dot-dash line indicates epinephrine alone. Solid line indicates epinephrine and glucose.

after administration of glucose in normal subjects[1,14] but a rise after parenterally injected epinephrine[6,15] or during fasting.[16] It is possible that epinephrine had no effect at all upon the metabolism of citrate, and that rises noted when epinephrine was injected without simultaneous administration of glucose were chiefly the result of fasting; this hypothesis needs further evaluation.

Certain findings that were statistically significant, though not highly significant, were obtained for which there is little explanation. The lower glucose curve in psychotic patients is contrary to expectation; however, the experiments on patients were carried out in their own rooms, whereas the control subjects had to come to the laboratory, sometimes after working during the night. The elevated citrate curve, as stated earlier, is a common finding in psychotic patients—one that has never been explained. The difference in shape observed between the pyruvate curves of controls and patients is also unexplainable but is of questionable physiological significance.

In the three subjects in whom tests with epinephrine alone, glucose alone, and epinephrine and glucose together were made, no attempt was made to evaluate the three curves statistically. In a few instances the curves obtained when glucose and epinephrine were given together appeared to represent an algebraic addition of the effect of glucose and epinephrine alone, but this finding was not constant. Failure of such a relationship was most strikingly demonstrated in the curves of citrate levels.

Elevation of blood reduced glutathione level after the administration of epinephrine confirmed earlier observations.[8,17] Although epinephrine is known to depress blood eosinophil cell counts markedly,[18] this phenomenon was not observed in the current experiment; the probable reason for this was the low dosage which was employed. The cause of the small fall of blood eosinophil counts during the experiments both with and without epinephrine is obscure. The decrease was not of sufficient magnitude to be of physiological importance, and should not be interpreted as being caused by excessive adrenal cortical activity.

The intravenous method of administration of epinephrine deserves comment. Use of this technique gives a reasonably uniform blood level of the hormone and also obviates the irregularities of effect due to varying absorption which occurs with intramuscular injection. Many of our subjects complained of anxiety during the first few minutes of epinephrine infusion and some showed cold extremities throughout the test. None, however, exhibited anxiety throughout the full three hours, and, in the patients, other psychiatric symptoms were not aggravated during the short period of the infusion.

It is highly significant that marked effects of epinephrine on carbohydrate metabolism occurred in these studies, despite the fact that pulse and blood pressure levels were largely kept at control levels. This dissociation of the effects of epinephrine on carbohydrate metabolism from those on cardiovascular change was noted in animal experiments by Cori et al.,[19] who observed that effects upon carbohydrate metabolism occurred at dosages approximately one-tenth as large as those necessary to obtain pulse and blood pressure changes. However, this

group was unable to confirm such a dissociation of physiologic and metabolic effects in human subjects.[12]

The significance of the data reported in this paper for understanding the metabolic derangements that occur in psychotic patients cannot yet be evaluated. Nevertheless, the rate of endogenous epinephrine secretion in psychotic patients must play a part in determining the level to which the curves of blood glucose, lactate, pyruvate, and α-ketoglutarate rise after the ingestion of glucose; epinephrine does not appear to influence citrate metabolism.

The observed impairment of ketoacid metabolism produced by epinephrine is of particular interest in that this metabolic disorder appears to be correlated with mental dysfunction.[20,21] In the present experiments, however, there was no such parallelism between the degree of impairment of ketoacid metabolism and mental symptoms, probably because of the short duration of the epinephrine infusions; nevertheless, it is possible that the prolonged hypersecretion of epinephrine that occurs in mental disease [35] may aggravate psychiatric symptoms through this mechanism.

The present study has certain implications for general medicine. For example, the apparent worsening of diabetes that occurs with strong emotion might be due, at least in part, to the secretion of epinephrine. The metabolic consequence of this hypersecretion is to superimpose a second, fundamentally different, metabolic disorder on the diabetes; although the specific diabetic metabolic defect, which manifests itself by abnormally small rises in lactate and pyruvate after ingestion of glucose,[13,28] is not worsened, the glycosuria becomes more severe. Similarly, the apparent aggravation of diabetes that often occurs during or after myocardial infarction, cerebrovascular accidents, infections, and surgical operations may be due in part to a similar mechanism, since increased secretion of epinephrine has been found in some of these conditions and probably occurs in the rest.

There are also other disorders in which abnormal elevations of blood glucose, lactate, and pyruvate levels occur in the fasting patient or after the administration of glucose (data on blood α-ketoglutarate levels are lacking except for thiamine deficiency, liver disease, and Cushing's disease, in all of which the metabolism of this substance is impaired). These conditions are various neurological disorders,[21,23,24] Cushing's syndrome,[25] cardiac and pulmonary diseases characterized by anoxia,[26,27] thyrotoxicosis,[30-32] thiamine deficiency,[28-30] and liver disease.[28,33,34] The enzymatic disorders associated with thiamine deficiency and with liver disease probably are sufficient causes for the associated disorder of carbohydrate metabolism. In the case of the others, it is possible that epinephrine hypersecretion is a factor.

It may be concluded, therefore, that hypersecretion of epinephrine may influence carbohydrate metabolism adversely in many diseases; its influence is most evident in diseases in which at least moderately severe disturbances of carbohydrate metabolism are already present.

Summary

The effect of the intravenous administration of epinephrine upon five carbohydrate moieties was studied in six normal and in six psychotic subjects over a three-hour period following ingestion of glucose. With epinephrine, blood concentrations of glucose, lactate, and pyruvate showed much greater rises and that of α-ketoglutarate a somewhat greater rise than without epinephrine. No significant effect of epinephrine in the change in plasma citrate level after glucose was observed.

The effect of epinephrine on carbohydrate metabolism did not represent merely the combined effects of epinephrine and glucose. Epinephrine infusion raised blood-reduced glutathione levels significantly but had no effect on eosinophil levels, probably because of the small dosage employed.

Abnormalities of carbohydrate metabolism similar to those caused by epinephrine

are observed in many psychotic patients and also in a variety of organic disorders.

At least four mechanisms—anoxia, thiamine deficiency, excessive adrenal cortical activity, and excessive adrenal medullary activity—appear to cause similar changes in carbohydrate metabolism.

McLean Hospital.

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Needle Biopsy of the Peritoneum

A Preliminary Report

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The surgical removal of diseased tissue from the body and subsequent careful examination by histologic, biologic, and even chemical analyses has greatly enhanced our understanding of the etiology and pathophysiology of many disease entities. Furthermore, it has provided the clinician with a rational foundation for specific therapy, replacing regimens previously employed, many of which had been based solely on empirical principles. In recent years, the introduction of the Vim-Silverman or similar type biopsy needles, combined with the resurrection and reevaluation of needle aspiration techniques, has provided us with invaluable information especially in hepatic and renal disease. Smetana [1] recently reviewed the experiences with specimens obtained by needle biopsy submitted for pathologic study and concluded that this procedure, properly and judiciously employed, has distinct advantages over many presently accepted diagnostic techniques. Since the first report of serous membrane needle biopsy, by DeFrancis,[2] in 1955, others have reported more extensive studies of pleural biopsy.[3-7] During the past year we have applied a similar approach to the study of patients with various types of intra-abdominal disease with ascites by attempting punch biopsies of the peritoneum. To our knowledge, needle biopsy of the peritoneum has not previously been reported. The method of peritoneal biopsy, the indications, and the results, together with selected clinical cases, form the basis for this preliminary report.

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Indications and Contraindications

The prime indication for peritoneal biopsy would seem to be those clinical situations in which the peritoneum per se is involved, by either an infection or a neoplastic process. The situation is somewhat analagous to pleural effusion, since the pathogenesis of peritoneal involvement is either due to contiguity from diseased nodes or organs, lymphatic spread, or hematogenous dissemination. Auerbach,[8] in 1950, reviewed this problem with respect to tuberculosis, and others [9,10] have commented on this with respect to malignant involvement from various sites.

At present we have considered only the following indications, but as further experience is gained there well may be additions and deletions. Biopsy was performed (1) to supplement the study of the ascitic fluid removed and in an attempt to correlate the histologic changes when present with the clinical course; (2) to attempt to avoid

exploratory laparotomy in patients in whom biopsy without resection would be required, or in those in whom the information obtained would not warrant such a formidable procedure; (3) to attempt to establish a histologic diagnosis in those patients in whom laparotomy would be medically contraindicated and in whom no other possible site for biopsy was available.

The potential dangers attendant with this procedure are those associated with abdominal paracentesis in general, i. e., hemorrhage, perforation of the bowel, infection, or spread of malignancy. Bleeding in those persons without blood dyscrasia is rare; perforation is uncommon unless adhesive peritonitis is present; infection is of minor significance (rarely seen in either therapeutic pneumoperitoneum or abdominal paracentesis), and spread of malignancy is also unimportant, since peritoneal involvement is probably already present. The prime contraindication of technical importance, however, is the absence of ascitic fluid. Although perforation of the bowel is uncommon, even when a needle is introduced to induce either a therapeutic or diagnostic pneumoperitoneum, it is logical to assume that it would be even more rare if fluid is present. Furthermore, as in pleural biopsy, the presence of fluid is utilized to localize the position of the serous membrane. The creation of an artificial pneumoperitoneum could also be utilized as a precautionary measure similar to pneumothorax. To date, however, we have not employed this procedure.

Clinical Material

Fourteen patients with historical evidence of intra-abdominal disease and in whom the physical examination was compatible with the presence of free fluid in the peritoneal cavity were selected for study. The biopsy was performed at the time of paracentesis and in all patients was utilized in conjunction with all the other usual diagnostic studies. In no patient had the diagnosis been verified by any other method prior to biopsy. However, previous operative procedures had established the existence of disease of intra-abdominal origin in three patients. In none of these cases had either ascites or peritoneal involvement been present at the time of the original diagnosis. Eleven of the group were thought to have ascites secondary to peritoneal metastases, and the remaining three were thought to be idiopathic in origin, although the suspicion of tuberculosis was high in this group. No patient in whom the cause of ascites was obvious was included; however, now that the procedure appears to be a safe and simple one, its application to other clinical entities seems warranted.

Method

The patient is placed in the position utilized for a routine paracentesis so that maximum tension is exerted on the anterior abdominal wall. The site is selected and prepared in the usual manner, with observation of the same precautions. With use of local anesthesia, the skin and subcutaneous tissue are infiltrated down to the peritoneum. The peritoneal cavity is then entered with use of the same apparatus as is commonly used for chest taps. After appropriate amounts of fluid have been obtained for necessary studies, the needle is withdrawn until the flow of fluid suddenly ceases. A Kelly clamp is then attached at skin level. The syringe and needle, with clamp attached is then withdrawn. This distance from the end of the needle to the clamp is then measured and transferred to the biopsy needle. The biopsy needle is then inserted into the anterior abdominal wall up to the clamp. This theoretically places the edge of the needle at the peritoneum. The obturator is withdrawn, and the biopsy shaft is slowly inserted until resistance is encountered. At this point, the patient is encouraged to further increase intra-abdominal pressure and simultaneously the shaft is advanced to the hilt. The outer sleeve is then advanced, and the shaft is rotated 360 degrees and then withdrawn. The same puncture site may be used for several biopsies by varying the direction of the needle.

After the initial few cases were biopsied, it became obvious that an alternate method may be employed. After infiltration, the biopsy needle with obturator in place can be introduced into the peritoneal cavity. The obturator is removed and the outer sleeve is slowly withdrawn until the fluid suddenly ceases, which also should approximate the level of peritoneum. Then the shaft is introduced until the resistance is encountered. The remainder of the procedure is the same.

Results

Of the 14 patients in whom the procedure was performed, tissue, representing peritoneum (Fig. 1), was obtained in 12. More significant, however, was the fact that a

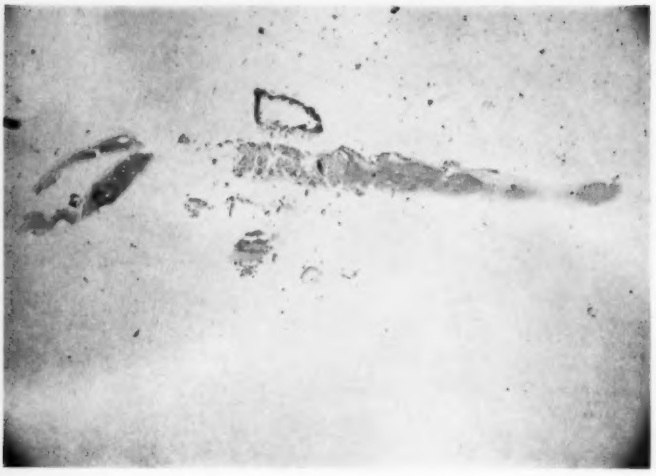

Fig. 1.—Microscopic section of peritoneal tissue obtained by biopsy with use of the Vim-Silverman needle. Although grossly small, it is more than adequate to establish a histologic diagnosis as evidenced in this section; reduced 40% from mag. × 9.

TABLE 1.—*Types of Cases Studied*

	Cases, No.	Positive Biopsy
Ascites ? due to malignancy	11	5
Ascites ? due to other disease	3	1
Total	14	6

specific diagnosis was delineated in six (50%) (Tables 1 and 2). Five demonstrated malignant changes and in the other a caseating granuloma was apparent. The correlation with histologic and cultural studies of the ascitic fluid is categorized in Table 3. In four of the six cases in which the biopsy was positive, the ascitic fluid did not yield any evidence of malignant cells or cultural evidence of tuberculosis. In two cases, both the fluid and the biopsy were positive, demonstrating malignant changes. In the remaining six cases in which peritoneum was obtained but was normal the fluid also

TABLE 2.—*Results of Needle Biopsy of the Peritoneum*

	Cases, No.
Diagnosed by biopsy	6
Normal peritoneum	6
Inadequate tissue	2
Total	14

TABLE 3.—*Correlation of Ascitic Fluid and Peritoneal Biopsy*

Diagnosis	Pos. Ascitic Fluid, Pos. Biopsy	Neg Ascitic Fluid, Pos. Biopsy	Neg. Ascitic Fluid, Neg. Biopsy
Carcinoma	2	3	6
Tuberculous peritonitis		1	2

was not diagnostic. All six were subsequently proven to have malignancy or tuberculosis either at laparotomy or at postmortem examination. Thus it would appear that there were six patients in whom the biopsy was not of value in establishing the final diagnosis. The remaining two patients in whom no peritoneal tissue was obtained were also subsequently proven to have ascitic effusion secondary to widespread carcinomatosis but no evidence of peritoneal studding.

Report of Cases

CASE 1.—This 48-year-old Negro woman was admitted to the hospital in January, 1957, with a history and physical examination compatible with intestinal obstruction. After appropriate studies, an exploratory laparotomy was performed; carcinoma of the transverse colon was detected, and resection was carried out. There was neither gross nor histologic evidence of involvement of the liver, peritoneum, or omentum. The postoperative course was uncomplicated, and in February, 1957, discharge was accomplished. Four months later

Fig. 2.—Section of the peritoneum in Case 1, which demonstrates undifferentiated carcinoma; reduced 40% from mag. ×225.

she was readmitted with abdominal swelling, anorexia, and weight loss. On physical examination ascites was present. Paracentesis yielded 1,000 cc. of bloody fluid, which did not contain any malignant cells. The peritoneal biopsy (Fig. 2) findings were compatible with undifferentiated carcinoma involving the peritoneum. At autopsy, 16 weeks later, there was diffuse peritoneal seeding.

Case 2.—This was a 54-year-old Negro woman admitted to the Medical Service with painful abdominal swelling, anorexia, and progressive dyspnea of five months' duration. Past history revealed the presence of adenocarcinoma of the ovary, established in 1952 by exploratory laparotomy. This was resected, and subsequently she was treated with x-ray. On physical examination there was evidence of ascites, and a peritoneal biopsy (Fig. 3) and paracentesis were performed simultaneously. There were malignant cells demonstrable within the fluid and areas of adenocarcinoma in the peritoneal specimen obtained by biopsy.

Comment.—In both of these cases the clinical impression was obviously metastases from the previously detected malignant lesion. In Case 1, however, biopsy was the first and only confirmation, and in the second it was available as quickly as the cell block, and probably more accurate. It also permitted immediate therapy with chemotherapeutic agents.

Case 3.—This 60-year-old Negro woman was admitted with a three-month history of anorexia, weight loss, and abdominal swelling. On physical

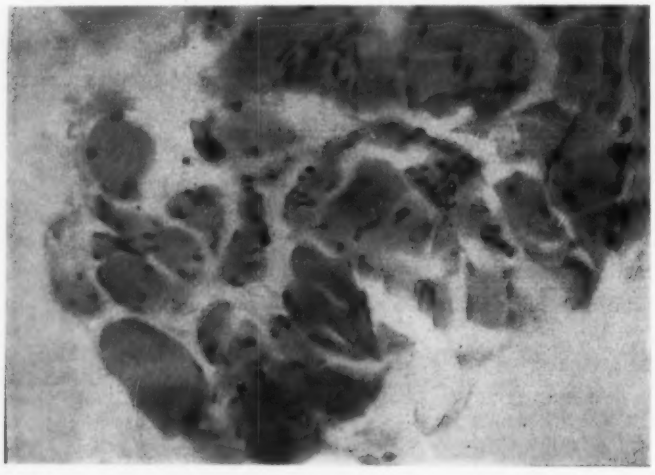

Fig. 3.—Adenocarcinoma involving the peritoneum which had metastasized from ovary. This specimen, also obtained by needle biopsy and under high power, is readily appreciated; reduced 40% from mag. ×225.

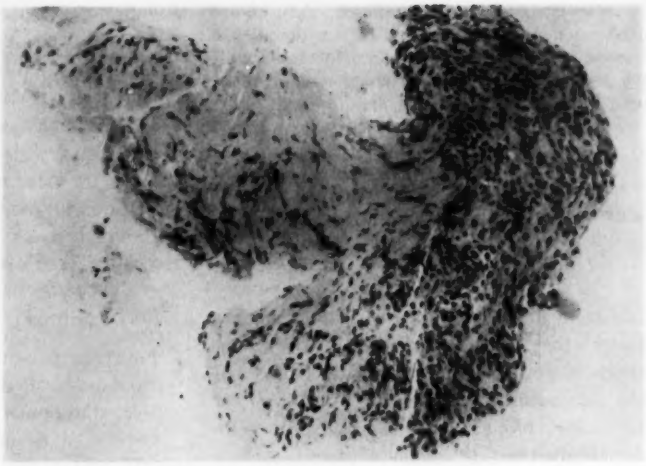

Fig. 4.—Photomicrograph of peritoneum in Case 3, showing metastatic adenocarcinoma from the stomach; reduced 40% from mag. ×70.

examination, in addition to the ascites and hepatomegaly there were signs of consolidation of the right lower lobe, which was confirmed by x-ray. Abdominal paracentesis was performed on two occasions, and the fluid did not contain any atypical cells. Biopsy was carried out at the second tap (Fig. 4) and demonstrated metastatic adenocarcinoma of the peritoneum. Despite appropriate antibiotic therapy for the pneumonia, the patient died shortly thereafter and carcinoma of the stomach with metastatic involvement of the peritoneum was in evidence.

Comment.—In addition to supplying the diagnosis extremely early in the hospital course of this patient, tissue evidence was available which could not have been obtained through surgical approach because of contraindications. This is not dramatically emphasized here, since death occurred anyway; however, there are many other situations in which laparotomy may be contraindicated.

Case 4.—This 26-year-old Negro male student was admitted to the Pulmonary Disease Division with a six-week history of crampy abdominal pain associated with diarrhea and abdominal swelling. The intermediate PPD was positive, and other than the ascites the physical examination was unremarkable. Abdominal paracentesis was performed, and 1,000 cc. of serous fluid was removed which contained no malignant cells and was negative for the presence of tubercle bacilli both on smear and subsequently on culture. Biopsy of the peritoneum (Fig. 5) revealed a granuloma

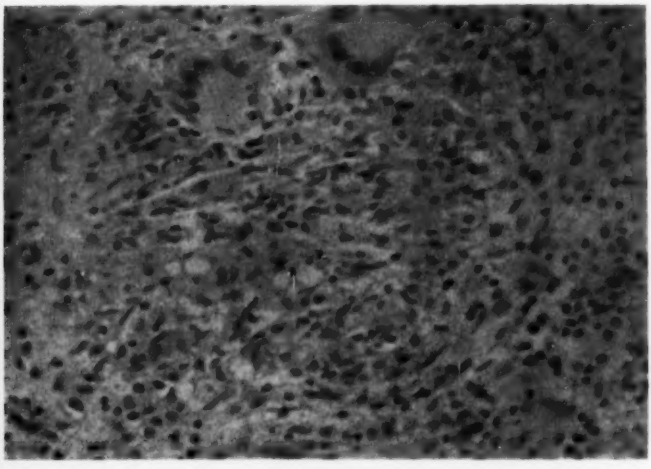

Fig. 5.—This histologic section demonstrates a granuloma with caseation necrosis, obtained in Case 4; reduced 40% from mag. ×225.

with areas of caseating necrosis. At surgical exploration one week later there was gross and histologic evidence of tuberculous involvement of the peritoneum. Appropriate therapy was instituted with an excellent response.

Comment.—The clinical diagnosis was well established before biopsy; however, in similar instances aspiration biopsy could prevent an unnecessary surgical procedure.

Comment

Smetana [1] has enumerated the multiple factors that must be appraised in the evaluation of any new diagnostic procedure and has also outlined the general indications for aspiration biopsy. When compared with previously existing methods, any procedure that (1) can supply a similar or greater amount of information, (2) may be performed more readily with the same or less morbidity, (3) is more economical, and (4) is of comparable accuracy, should rightfully supplant the other methods. The significance of these statements has been adequately demonstrated in regard to the value and use of liver [1] and renal-aspiration biopsy techniques.[11,12] These are currently preferred to the usual surgical methods for obtaining biopsy specimens of these organs.

It has been our impression that in patients with intrathoracic disease associated with pleural effusions, aspiration biopsy is a preferred technique initially and surgical biopsy may be avoided in approximately 75% of the cases studied.[6] At the present time we cannot apply this reasoning to biopsy of the peritoneum. On the basis of our preliminary studies, certain major objections, however, would seem to have been eliminated. This technique is safe and easy to perform; it is economical and less of a problem than those requiring a surgeon, anesthetist, and operating room facility. The question of accuracy and its validity as a diagnostic procedure will only be established by further study.

It must be kept in mind that punch biopsies can only reflect the histologic changes demonstrable in the focal area from which the biopsy is obtained and that serous membranes frequently reflect no histologic changes or those of a nonspecific nature, when either involvement does not exist or is not diffuse. It would seem reasonable, however, on the basis of this preliminary report, to suggest a widespread trial of needle biopsy of the peritoneum and to establish the limitations and efficacy of this approach to the diagnosis of intra-abdominal diseases associated with ascites.

Summary and Conclusions

Fourteen patients with varying types of intra-abdominal disease and ascites were subjected to punch biopsy of the peritoneum.

Peritoneal tissue was obtained in 12 of the 14, and in 50% a specific diagnosis was demonstrable on histologic section. The diagnosis was corroborated in all by other methods. In the other 50% normal peritoneal tissue was obtained.

No complications were encountered in any patients.

The procedure is safe and simple and would seem to be as accurate as any punch biopsy when properly and judiciously employed.

Although only a preliminary report has been presented, further experience with this new approach to the diagnosis of intra-abdominal disease seems warranted.

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The Diuretic Response to Administered Water in Patients with Liver Disease

I. Acute Infectious Hepatitis

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The extensive literature concerned with the urinary excretion of water and solute in patients with liver disease has recently been reviewed.[1] Although many reports describe impairment of water excretion in acute infectious hepatitis,[2-5] there are few observations concerned with the determination of maximal diuretic response to administered water in conjunction with measurement of glomerular filtration rate and solute excretion. Accordingly, the acute renal response to water loading was investigated in ten patients with active viral hepatitis. In all, during the acute phase of the disease, a normal diuretic response to water administration was demonstrated.

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Material and Methods

The patients, men varying in age from 21-34, were studied during the acute phase of viral hepatitis as diagnosed by clinical and laboratory criteria. Certain relevant data concerning the patients are shown in Table 1. Eight of the patients were studied within three days of admission before any improvement in clinical or laboratory manifestations had occurred. Patient 1 was studied after his serum bilirubin had declined from the admission value. Patient 5 was studied early in his course and once again shortly before death. The jaundice in Patient 9 was increasing at the time of the study and continued to do so for several days.

A water load of 20 ml. per kilogram of body weight was administered orally or intravenously (4% invert sugar) during a 30-minute period. In Patients 1-5 each route of administration was employed on separate occasions. The administered

TABLE 1.—*Clinical Data on Patients with Acute Infectious Hepatitis*

		Duration Before Admission *			Serum Bilirubin, Mg/100 Ml.		
Patient	Age	Symptoms	Jaundice	Dark Urine	Day of Study	Maximum During Illness	Duration of Elevated Serum Bilirubin (>1.4 Mg/100 Ml.), Days
1	31	6	3	5	2.4	4.0	> 8
2	29	7	1	5	4.4	4.4	>20
3	26	6	7	7	15.8	15.8	>22
4	21	2	1	3	11.0	11.0	>10
5	27	3	1	?	18/26	45.0	57; death
6	27	4	--	3	2.6	2.6	< 7
7	27	5	5	5	3.2	3.2	7
8	34	7	7	10	10.4	10.4	< 7
9	30	14	1	10	9.6	15.2	>42
10	26	14	7	10	13.8	13.8	>17

* Days of symptoms, observed jaundice, and observed dark urine.

load was sustained by providing sufficient water after each voiding to maintain body weight constant. In the studies in nine patients the urine was voided at intervals not exceeding 30 minutes for a sufficient length of time to observe the peak rate of flow. Analyses for total solute, sodium, potassium, chloride, and creatinine were performed on at least two specimens by methods previously described from this laboratory.[6,7] Venous blood drawn at the height of diuresis was similarly analyzed.

Results (Table 2)

1. Maximal observed urine flow varied from 9.4 to 23.3 ml. per minute and was attained in each instance within 86 minutes after water loading. In three of the five patients tested by both routes of loading the diuretic response to the intravenous load was slightly greater than when the water was taken orally.

2. Urine osmolality at the height of diuresis was low, ranging from 38 to 77 mOsm., except in the second experiment in Patient 5, described below. Total solute excretion varied between 0.456 and 1.800 mOsm. per minute during peak diuresis.

3. The rate of sodium excretion during "maximal" diuresis varied from 23-290μEq. per minute. Chloride excretion in the same period was 25-237μEq. per minute, while potassium excretion ranged from 21-127μEq. per minute. Creatinine clearance was within normal limits in all instances, ranging from 124-232 ml. per minute.

4. Patient 5, whose initial diuretic response to an oral load was 12.7 ml. per minute with a concentration of 36 mOsm. per kilogram of water, had an unfavorable course and died of acute hepatic necrosis. Two days before death the maximum flow achieved after intravenous loading was 7.5 ml. per minute and the lowest osmolality was 101 mOsm. Creatinine clearance was within normal limits during both tests.

Comment

It is apparent that in all 10 patients studied during the acute phase of infectious hepatitis the diuretic response to water administration was quite comparable to that attained by normal subjects.[7,8] Only in the one gravely ill patient restudied just prior to death, when discomfort alone may have stimulated the secretion of antidiuretic hormone, was there a modest impairment in water diuresis. It is also clear from the low urinary solute concentrations observed that there was no demonstrable impairment in the capacity to inhibit antidiuretic hormone secretion with water administration, and, since the onset of maximal rates of flow was prompt, there was no delay in eliminating antidiuretic activity.

Attempts to reconcile these observations with previous ones is difficult. In some reported studies sufficiently detailed data for comparison are not provided. In other studies, for example that of Adlersberg and Fox,[4] the cases studied may well have been quite different from ours. Their 23 patients were not a homogeneous group but rather consisted of patients with a variety of parenchymatous liver diseases. The specific case reports provided were of patients sick for at least two months before study. On the other hand, the 14 patients described by Labby and Hoagland[5] seem very similar to our group in severity of illness and the time of the study in the course of the disease. The major obvious difference in their study and the one reported here is the fact that they did not utilize a sustained water load, although it seems unlikely that this difference alone would account for the discrepant results. Data concerning solute excretion and filtration rate are not available to determine the nature of the observed impairment in the Labby and Hoagland report. It seems probable that the discrepancies observed are related either to the precise details of experimental design or to differences in the patients selected for study (severity of illness, stage of the disease, and perhaps even the specific variety of acute infectious hepatitis), although these differences are not readily apparent.

Some investigators have described renal functional disturbances in terms of decreased clearance of creatinine and urea and impairment of urinary concentrating ability.[9-11]

TABLE 2.—*Additional Data on the Patients*

Patient No.	Hospital Day	Route	Elapsed Time * Min.	Urine								Clearances		
				Flow, Ml/Min.	Total Solute		Sodium		Potassium		Chloride		Creatinine, Ml/Min.	Osmolar, Ml/Min.	Free Water, Ml/Min.
					mOsm/L.	μOsm/Min.	mEq/L.	μEq/Min.	mEq/L.	μEq/Min.	mEq/L.	μEq/Min.			
		P. O.	32–62	19.3	42	810	7.1	137	6.6	127	7.5	145	183	2.8	16.5
	6		62–93	18.6	38	710	7.3	117	7.0	130	8.1	151	189	2.5	16.1
1		I. V.	2–30	23.3	77	1,800	12.4	290	4.1	96	10.2	237	232	6.2	17.1
	7		30–61	20.4	71	1,450	11.0	224	4.5	92	10.4	212	230	5.0	15.4
			0–25	8.8	103	910	6.9	61	5.6	49	8.5	75	144	3.3	5.5
		I. V.	25–45	10.7	65	695	3.9	42	3.7	40	4.2	45	132	2.5	8.2
	2		45–65	13.5	61	820	4.3	58	3.2	43	4.1	55	142	2.9	10.6
2			25–55	10.3	82	841	2.8	29	9.2	95	5.1	52	135	3.0	7.3
	3	P. O.	55–75	12.0	63	756	2.9	35	10.3	124	4.5	54	122	2.7	9.3
			75–97	13.4	54	722	3.1	42	9.2	123	4.9	66	141	2.6	10.8
		P. O.	42–72	9.4	51	479	1.3	12	3.5	33	3.1	29	139	1.7	7.7
	2		72–102	8.7	48	416	1.0	9	3.4	30	2.5	22	128	1.5	7.2
3	3	I. V.	6–36	12.5	78	975	3.6	45	5.7	71	3.5	44	135	3.5	9.0
			36–66	13.9	62	860	3.3	46	4.7	65	3.0	42	128	3.1	10.8
	4	P. O.	49–79	11.3	48	541	2.0	23	3.5	40	2.8	32	126	1.9	9.4
			79–109	10.2	42	430	1.2	12	3.1	32	2.1	21	110	1.5	8.7
		I. V.	9–39	12.8	61	780	3.5	45	2.5	32	5.4	69	153	2.8	10.0
	2		39–60	15.0	56	840	4.0	60	2.1	31	5.0	75	155	3.1	11.9
4		P. O.†	0–41	8.1	91	735	5.9	48	4.9	40	10.9	88	168	2.6	5.5
	3		41–80	8.4	89	748	6.8	57	2.5	21	10.8	91	170	2.7	5.7
			49–79	11.8	39	459	2.6	31	4.4	51	4.1	48	121	1.7	10.1
	10	P. O.	79–109	12.7	36	456	2.8	36	5.2	66	2.0	25	124	1.6	11.1
5	55	I. V.	11–43	7.5	101	760	9.8	73	9.1	69	14.8	111	117	2.7	4.8
		P. O.	29–59	20.9	52	1,090	9.5	199	4.3	90	10.0	209	197	3.8	17.1
6	3		59–89	21.1	44	928	6.9	146	3.3	70	6.7	141	193	3.3	17.8
			2–22	12.5	70	871	4.3	54	2.1	26	2.5	31	146	3.1	9.4
7	1	I. V.	22–42	13.6	58	789	4.0	53	1.9	26	2.5	34	142	2.8	10.8
8	2	P. O.	61–86	15.9	66	1,048	9.0	142	2.3	36	12.3	196	206	3.7	12.2
			30–58	10.8	78	842	5.1	55	10.5	113	5.2	55	158	2.9	7.9
			58–86	7.7	99	762	9.5	73	14.3	111	8.3	64	144	2.6	5.1
9	3	P. O.	86–115	7.1	130	923	14.5	103	15.1	107	12.8	91	157	3.2	3.9
			115–145	13.3	71	945	9.4	125	7.6	101	5.9	79	166	3.3	10.0
			145–171	11.3	75	848	9.5	107	7.8	88	6.9	78	149	2.9	8.4
			12–21	20.6	47	970	2.2	45	4.5	92	5.5	113	205	3.6	17.0
10	3	P. O.	21–41	19.8	41	810	1.6	32	4.8	95	5.0	99	189	3.0	16.8

* Time from completion of the initial administration of the water load.

† Nausea during the experiment prohibited maintenance of the load.

In the present study creatinine clearance was well within the normal range in all patients, including one who died of his disease a few days after the second test was performed. This patient, who failed to achieve as high a flow rate as in the first study, had ascites at the time of this second test.

The present study thus does not confirm other reports describing impairment of water diuresis and diminution in filtration rate in patients with acute infectious hepatitis. Regardless of the precise reasons for the discrepancies in observations, it is apparent that acute hepatic functional impairment is not *necessarily* associated with a reduced glomerular filtration rate or an impaired capacity to respond normally to administered water.

Summary

The response to water loading has been investigated in 10 patients with acute infectious hepatitis.

Maximal urine flow was attained without delay and varied from 9.4 to 23.3 ml. per minute.

Urine osmolality, at the height of diuresis, ranged from 38 to 77 mOsm.

Creatinine clearance was within the limits of normal in each instance.

In all 10 patients studied during the acute phase of infectious hepatitis, a normal diuretic response to water administration was demonstrated. Modest impairment was observed in one gravely ill patient studied just prior to death.

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The Diuretic Response to Administered Water in Patients with Liver Disease

II. Laennec's Cirrhosis of the Liver

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While it is stated that the diuretic response to water loading in patients with hepatic cirrhosis is often impaired,[1] there are several reports suggesting that striking limitation in water excretion is not a common finding.[2-5] Much of this literature is reviewed elsewhere.[6] In the course of searching for patients suffering from cirrhosis who had limited ability to excrete administered water, we were impressed with their relative rarity despite the fact patients with cirrhosis are not uncommon in this area. This report records the study of 48 patients with cirrhosis and includes an attempt to correlate the capacity to excrete administered water with the clinical condition of the patient and some parameters of renal function. The data suggest that, with the exception of a number of seriously ill patients, most patients with cirrhosis have significant diuretic responses to administered water.

Methods

Patients with hepatic cirrhosis were studied subsequent to breakfast in the morning after the administration of a large oral * water load, which was sustained until it became apparent that no further augmentation of urine flow was likely. Only patients whose daily weight was stable or increasing were included in the study in an effort to exclude those patients who might be undergoing spontaneous diuresis. Several patients were studied on more than one occasion.

Diets varied in sodium content from 10 mEq. per day to regular hospital fare with salt permitted freely. During study the patients remained recumbent except for standing to void. Venous blood was obtained one or more times after the administration of the water load during the course of each experiment. Either a standard water load of 1,500 ml. or one of 20 ml. per kilogram of body weight was administered within a 45-minute period. The load was maintained by having the patient drink a volume of water equal in amount to each voiding. In all patients the urine and blood specimens were analyzed for creatinine content and the creatinine clearance was calculated. In 34 of the 48 patients serum sodium, potassium, chloride, and total solute concentrations were determined. In 19 patients the urine was also analyzed for sodium, potassium, chloride, and total solute content.[5,7] Serum albumin and globulin concentrations were determined in 28 persons.

Results (Tables 1, 2, and 3)

1. *Maximal Urine Flow.*—Eight subjects (Patients 1-8) had a maximal urine flow after water loading of less than 4 ml. per minute. Eighteen additional subjects (Pa-

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* Three patients were given the water load intravenously as 4% invert sugar.

TABLE 1.—*Patients with Maximal Urine Flow Less than Four Milliliters per Minute*

Patient No.	Age, Yr.	Dietary Sodium, mEq/24 Hr.	Clinical Appraisal			Serum						Urine *				
													Solute			
			Ascites	Edema	General Condition †	Bilirubin, Mg/100 Ml.	A/G, Gm/100 Ml.	Sodium, mEq/L. ‡	Potassium, mEq/L. ‡	Chloride, mEq/L. ‡	Solute, mOsm/L. ‡	Flow, Ml/Min.	mOsm/L.	μOsm/Min.	Sodium, μEq/Min.	Clearance Creatinine, Ml/Min.
1	46	10	4+	0	3+ (d)	3.2	2.7:3.8	128	4.0	97	282	3.3				105
2	65	10	4+	2+	4+ (d)	33.6		122	3.9		260	0.4				18
3	61	25	4+	1+	4+ (d)	6.6	2.7:2.9	126	3.5	96	263	1.4	149	223	<1	67
4	61	Regular	4+	0	4+	3.8		121	4.9		270	0.5				132
5	41	Regular	4+	1+	4+ (d)	5.3		135	4.1		277	1.0	458	567	2	156
6	50	10	4+	2+	4+ (d)	6.8						3.3				134
7A §	46	10	4+	2+	4+ (d)	5.8	1.8:4.8	118	3.0	81	248	1.0	262	290	<1	117
7B	46	10	4+	1+	4+ (d)	0.2	1.9:4.4	116	4.5	92	245	0.7	260	240	<1	87
7C	46	10	4+	1+	4+ (d)	0.2	2.1:4.6	112	4.8	88	246	0.5	542	284	<1	93
8C ‖	54	10	4+	3+	4+ (d)	1.0	1.7:4.5	126	3.3	96	263	2.5	149	375	2	114
8D	54	10	4+	0	4+ (d)	0.6	2.6:4.2	124	5.2	96	260	2.1	178	388	<1	81

* Values during period of maximal flow.
† Extremely ill-appearing, 4+; moderately ill, 3+; minimally ill, 2+; virtually asymptomatic, 1+; (d) indicates died (see text).
‡ Values after water load established.
§ 7A and 7B are experiments 2 mo. apart in the same person; 7C is 1 wk. after 7B.
‖ 8C is 5 mo. before 8D.

tients 9-26) and Patient 8 earlier in the course of the disease had a maximal flow of 4-9 ml. per minute. Another 22 subjects (Patients 27-48), as well as Patients 15 and 20 later in their course, had a peak flow greater than 9 ml. per minute in response to the water loading.

2. *Clinical Appraisal.*—In general, the eight subjects with striking impairment of diuretic response to ingested water appeared to be among the most severely ill in terms of general clinical appraisal. Indeed, seven of the eight patients have died in hepatic coma within a period of 20 months of the study. Of these, four deaths occurred less than two months after the last experiment; two, within 8 months, and one, 20 months later. In all but one instance hepatic coma was preceded by gastrointestinal bleeding. The course of the eighth patient with poor diuretic response is not known to us at this time. The patients who achieved higher rates of urine flow were in general less seriously ill. Of these 40 patients, 5 have died in coma, 1 within 3 weeks of the study and the other 4 from three to 12 months later. One of these patients (Patient 13), who achieved a flow of 6.8 ml. per minute when first studied, had a peak flow of less than 1.0 ml. per minute when restudied three months later, one week prior to death in hepatic coma. On the other hand, there were striking exceptions in that several patients who appeared extremely ill were able to achieve significant diuretic response to water loading. All the patients with peak flows of less than 4 ml. per minute had extensive ascites. However, similar degrees of ascites did not preclude the ability to have a greater diuretic response to water. Similarly, the degree of jaundice did not have any consistent relationship to maximal flow.

3. *Creatinine Clearance.*—While endogenous creatinine clearance was generally lower in the poor response group, in several instances peak flows of less than 4 ml. per minute were associated with normal creatinine clearance. In most of the remaining patients studied, including other severely ill patients, the creatinine clearance was over 100 ml. per minute and no precise correlation with urine flow was apparent.

4. *Serum Sodium Concentration.*—In general the serum sodium concentration and serum osmolality tended to be lowest in those patients who had greatest impairment in the diuretic response to water. Thus seven of the eight patients with the poorest diuresis had serum sodium concentrations after water loading of 128 mEq. per liter or less, while no one in the group whose flow exceeded 9 ml. per minute had a serum sodium concentration quite this low.

5. *Excretion of Total Solute and Sodium.* Although the data are limited, in general the poor response group had more striking restriction of the renal excretion of total solute and sodium than the patients with greater diuresis.

Comment

It is apparent from these observations as well as from those of other investigators that in patients with cirrhosis of the liver, whether "compensated" or "decompensated," there is considerable variability in the diuretic response to a water load.[1-6,8] Few patients, however, exhibit striking impairment.

An attempt to delineate the clinical features of the disease that may be associated with the poorer diuretic responses was not fruitful, save for the fact that all the patients with the more marked impairment were extremely ill. Many of them died within a few months after the study. However, some equally sick patients exhibited little impairment in diuretic response. An attempt to define "extremely ill" in more precise terms was equally fruitless.

Although all the patients with poor diuretic responses had marked ascites, others with equally massive peritoneal collections had little or no impairment in diuresis. Moreover, Birchard et al.[5] noted severe restriction in water excretion in a seriously ill man with minimal ascites but deep jaundice. They reported another patient with marked impairment in diuresis who

TABLE 2.—*Patients with Maximal Urine Flow of Four to Nine Milliliters per Minute*

Patient No.	Age, Yr.	Dietary Sodium, mEq/24 Hr.	Clinical Appraisal			Serum						Urine *				
													Solute			
			Ascites	Edema	General Condition †	Bilirubin, Mg/100 Ml.	A/G, Gm/100 Ml.	Sodium, mEq/L. ‡	Potassium, mEq/L. ‡	Chloride, mEq/L. ‡	Solute, mOsm/L. ‡	Flow, Ml/Min.	mOsm/L.	μOsm/Min.	Sodium, μEq/Min.	Clearance Creatinine, Ml/Min.
8A §	54	10	4+	4+	4+ (d)	1.6	1.7:4.9	124	3.7	94	263	4.0	73	307	2	108
8B	54	10	4+	4+	4+ (d)	0.5	1.7:4.9	128	3.8	98	268	5.4	69	372	4	133
9	44	Regular	1+	0	2+	1.2	2.1:6.1	133	3.6	109	282	4.8	73	354	31	111
10	44	10	4+	0	2+		2.0:4.4	131	4.1	100	268	7.7	43	274	1	123
11	67	10	4+	1+	4+	4.0	2.6:6.1	134	4.4	99	277	5.4	66	365	11	136
12	35	50	4+	0	2+	6.0	2.2:4.2	128	4.1	98	260	6.0	79	504	7	172
13	42	10	4+	2+	1+ (d)	2.5	3.1:3.5	130	4.9	104	265	6.8	83	651	<1	146
14	56	25	2+	0	3+	15.4	2.9:3.8	133	4.0	101	271	8.3	43	360	27	106
15A	27	Regular	3+	1+	3+	15.0	3.5:2.8	117	5.3	96	242	8.0	76	605	<1	206
16	67	Regular	4+	2+	4+	3.0	2.7:4.5	128	4.4	102	266	4.0	93	612	1	197
17	47	25	1+	0	2+	9.4	3.9:3.2	133	4.9	100	266	6.2				168
18	49	Regular	4+	1+	4+ (d)	6.7		130	4.9	97	261	8.0				223
19	54	10	1+	0	2+	1.0		129	4.5		269	7.2				95
20A	59	10	4+	0	3+	0.6	3.2:3.0	144	5.4	98	279	9.2				106
21	30	Regular	1+	0	3+	3.2						7.8				196
22	56	Regular	3+	0	3+	1.8						6.3				103
23	56	Regular	3+	0	4+ (d)	5.0						5.0				66
24	43	Regular	0	0	1+	1.0						7.2				87
25	37	10	3+	0	3+	4.6						9.3				110
26	39	Regular	0	0	3+	2.4						9.3				

* Values during period of maximal flow.

† Extremely ill-appearing, 4+; moderately ill, 3+; minimally ill, 2+; virtually asymptomatic, 1+; (d) indicates died (see text).

‡ Values after water load established.

§ 8A is 2 wk. before 8B (8B is 1 wk. before 8C—Table 1).

had only mild icterus and massive ascites. Similarly, we failed to observe a distinct relationship between the severity of jaundice and the diuretic response to administered water.

Thus, although we cannot define specific clinical features of cirrhosis that characterize the poor response group, the data suggest that marked impairment in water diuresis may have serious prognostic significance. These studies alone, however, do not exclude the possibility of clinical improvement in patients with the greatest impairment in water diuresis.

Renal mechanisms which might be responsible for the inability of certain patients with cirrhosis to respond adequately to administered water include reduced glomerular filtration rate (GFR), increased antidiuretic hormone (ADH) activity, and diminished solute excretion. Although reduced GFR might be a factor in the poor diuretic response exhibited by several patients, other patients with equally inadequate water excretion had normal GFR.

The possible influence of ADH in limiting water diuresis in Laennec's cirrhosis has been considered in detail elsewhere[6] and will only be outlined in this discussion. While increased quantities of antidiuretic substances have been found in the urine of patients with cirrhosis and in vitro experiments have suggested decreased hepatic inactivation of ADH,[9-12] the precise significance of these observations remains unclear.[6,13-15] A consideration of physiological experiments had led us to conclude tentatively that while increased ADH activity may play a role in limiting water excretion in some patients with cirrhosis, it is not the prime mover. In addition, any increased ADH activity is more likely attributed to increased secretion of the hormone than to decreased inactivation. These conclusions were based largely on the folowing observations. Ethyl alcohol a specific ADH inhibitor, does not restore the blunted diuretic response to normal.[16,17] Increased diuresis may be achieved in some instances in association with increased solute excretion without further decline in urine osmolality, suggesting that the augmentation in flow occurred without further inhibition of ADH.[5] The following observations specifically fail to support the view that there is diminished inactivation of ADH in patients with cirrhosis. Maximum diuresis after water loading occurs very promptly in the cirrhotic; patients with cirrhosis achieve maximum urine flows after alcohol administration as rapidly as the normal person,[16] and the response to exogenous vasopressin (Pitressin) administration is entirely normal in these patients.[2-4] If there is increased ADH secretion, the mechanism by which this occurs is not entirely clear. Since serum osmolality is often reduced in patients with cirrhosis, it is apparent that any increased secretion of ADH must be attributed to a nonosmotic stimulus. The evidence that a decreased effective extracellular fluid volume may be a stimulus for increased ADH secretion in some patients with cirrhosis is considered in detail elsewhere.[6]

It is well known that a decreased solute load, especially a decrease in sodium excretion, will impose a limit on the diuretic response to administered water in the normal person.[18,19] While the mechanism of decreased sodium excretion in cirrhosis is not entirely clear,[6] several studies have served to emphasize the important role of this phenomenon in restricting water diuresis in these patients. Birchard et al.[5] observed that several patients with moderate impairment of water excretion after oral loading had a greater diuretic response when the water was administered intravenously. This enhanced response was associated primarily with increased excretion of sodium. In the studies of Strauss et al.,[16] the increased urine flow observed after the administration of hypotonic saline to patients with impaired water diuresis was also apparently related to increased solute excretion. Recently Schedl and Bartter[20] have reported an increase in free water clearance in patients with cirrhosis and impaired water diuresis when increasing quantities

TABLE 3.—*Patients with Maximal Urine Flow Greater Than Nine Milliliters per Minute*

Patient No.	Age, Yr.	Dietary Sodium, mEq/24 Hr.	Clinical Appraisal			Serum					Urine *				
			Ascites	Edema	General Condition †	Bilirubin, Mg/100 Ml.	A/G, Gm/100 Ml.	Sodium, mEq/L. ‡	Potassium, mEq/L. ‡	Chloride, mEq/L. ‡	Solute, mOsm/L. ‡	Flow, Ml/Min.	Solute		Sodium, μEq/Min.	Clearance Creatinine, Ml/Min.
													mOsm/L.	μOsm/Min.		
27	41	100	1+	1+	1+		2.8:4.2	133	3.7	101	274	10.0	66	770	147	116
28	62	100	1+	4+ §	1+		2.3:4.3	134	3.1	99	279	10.6	70	794	148	200
29	65	50	1+	1+	3+	1.2	2.6:5.1	129	4.1	100	279	14.3	53	1,780	122	156
30	40	25	4+	2+	3+	10.4	1.8:5.3	130	4.1	101	268	10.1	35	349	2	149
31	42	10	4+	4+	3+	1:8	3.3:3.7	132	3.8	99	260	9.1	48	437	32	192
23	59	10	2+	0	2+		2.0:3.9	140	4.0	111	287	16.9	40	676	48	171
33	26	Regular	2+	0	3+	33.0	3.3:2.8	140	4.8	102	281	27.9	27	817	45	165
34	31	25	1+	0	1+	2.0	3.1:3.7	140	5.1	101	275	17.8				193
35	42	10	2+	0	3+	20	2.9:3.6	140	4.4	106	283	14.6				133
36	41	Regular	1+	0	2+	4.3	3.1:3.5	135	4.4	106	282	12.8				171
37	47	Regular	3+	2+	3+	3.0	1.8:3.9	132	4.1	105	278	12.8				142
38	56	10	4+	4+ §	4+ (d)	7.0	2.0:4.5	132	5.3	98	272	9.9				162
39	53	Regular	3+	1+	4+ (d)	8.4	2.1:4.2	129	3.1	98	267	9.9				122
40	49	Regular	2+	0	2+	0.8	2.5:4.1	135	4.6	105	281	19.1				192
41	46	10	3+	0	4+	2.6		132	3.6	88	277	14.0				128
42	47	Regular	0	0	2+	1.2						11.4				126
43	35	10	2+	1+	3+	1.2						17.2				159
44	42	Regular	0	0	2+	0.2						13.7				176
45	39	25	1+	1+	3+	0.6						11.9				144
46	49	Regular	0	0	2+	2.5						16.4				155
47	61	10	2+	1+	2+	1.4						10.4				114
48	47	10	2+	2+	2+	1.0						14.4				154
15B ‖	27	10	3+	2+	3+	3.0	2.9:3.2	134	4.1	102	271	14.0	26	368	56	176
20B ‖	61	25	4+	0	3+	0.4	3.9:3.3	134	4.5	99	278	10.0	72	721	82	142

* Values during period of maximal flow.

† Extremely ill-appearing, 4+; moderately ill, 3+; minimally ill, 2+; virtually asymptomatic, 1+; (d) indicates died (see text)

‡ Values after water load established.

§ Chronic thrombophlebitis.

‖ Tests performed 2 wk. after No. 15A and No. 20A, respectively (Table 2).

of mannitol were substituted isotonically for dextrose in the infusion. These investigators postulated that mannitol, a nonreabsorbable solute, acted to decrease an excessive reabsorption of sodium and water in the *proximal* tubular segment in patients with cirrhosis, resulting in increased distal delivery of glomerular filtrate and consequent enhanced elaboration of "free water." Whatever renal mechanism may be involved, the increased excretion of water was apparently related to the solute load presented for excretion.

While the present data are too limited for firm conclusions concerning the role of solute excretion as a major determinant of the diuretic response to water, in general they are confirmatory in that the poor response group had more striking limitation in the excretion of total solute and sodium than the patients with greater diuresis.

The precise role of the reduced serum sodium concentration in patients with limited diuretic response is not clear from these data or those of Nelson and Welt,[3] who found a lower serum sodium concentration in patients with poor diuresis. It is possible that impaired water excretion may result in decreased serum sodium concentration in the event that the patient's water intake is in excess of his excretory capacity. On the other hand, it is certainly possible that no casual relationship exists between the two observations.

Summary and Conclusions

The diuretic response to administered water was studied in 48 patients with Laennec's cirrhosis of the liver.

Striking limitation in water diuresis is not a common finding in cirrhosis of the liver. A poor diuretic response tends to occur in the sickest patients, although not all extremely ill patients have strikingly impaired diuresis after water administration.

The maximal urine flow after water administration was not correlated consistently with the degree of ascites, the level of jaundice, or the endogenous creatinine clearance employed as an index of glomerular filtration rate. Limited diuretic response in general was associated with a reduced excretion of total solute and of sodium in particular.

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Benign Hypertension

A Study on 2,500 Cases

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Perhaps no other variation in the physiologic functions of the body has been subjected to as much investigation as has the blood pressure. The search for the cause of hypertension continues while newly discovered methods of therapy in hypertensive disease are being made available to those having this condition. Master et al.[1] defined hypertension, concluding that prior to 1952 the concepts were incorrect or misleading in that the critical levels established to divide normal from abnormal blood pressure were too low. The wide variations in blood pressure levels in a selected group of 1,522 patients with essential hypertension were observed over a long period by Hines.[2,3] Clinical hypertensive disease frequently developed among his subjects if the diastolic pressure was greater than 85 mm. Hg. Among the first observers to report on variable blood pressure and its apparently adverse effect on morbidity and mortality were Levy et al.,[4,5] in their studies on Army officers. Variable or so-called labile blood pressure has sometimes been regarded as an interesting physiologic phenomenon without serious implications.

The prognosis of the person with a health impairment is equally important to the practicing physician and the life insurance company. Medical statistical material exists on vast numbers of insured people, and a significant part of this is supplied by clinicians. The characteristics and practical usefulness of these statistics are described by Marks.[6] Their chief value to clinicians lies in the long-range follow-up aspect. Therefore, the ultimate evaluation of drugs recently popular and effective in hypertensive disease, of course, remains to be determined.

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Material and Method

The present investigation was made on material from the files of life insurance policyholders, who were required to pay increased premium rates because at least one blood pressure reading was above 136 mm. Hg systolic or 88 mm. Hg diastolic (Tables 1 and 2). All persons with any other condition that would also require an additional premium were excluded. Among these conditions were obesity or other metabolic disorders; demon-

TABLE 1.—*Mortality Experience on Insured Persons with Nonlabile and Labile Elevations in Blood Pressure*

Systolic Averages (on 2,023 Policies)			
Nonlabile (0-15 mm. Hg Range)	Mortality Percentage *	Labile (16 mm. Hg or Above)	Mortality Percentage *
130	183	130	152
140	247	140	250
150	162	150	252
160	219	160	0
170	303	170	2,000 †
180	0	180	0
Average	211	Average	237
Diastolic Averages (on 2,038 Policies)			
(0-12 mm. Hg Range)		(13 mm. Hg or Above)	
80	203	80	213
86	81	89	101
90	289	92	130
96	209	95	134
100	251	102	581
106	233	107	0
110	0		
Average	210	Average	185

* 100% mortality is representative of the substandard class to which the risk was assigned. From "Intercompany 1946-49 Select Mortality Table."

† Represents one very early death.

TABLE 2.—*Mortality According to Graduated Ranges of Variation in Blood Pressure*

Nonlabile, Range in Mm. Hg	Mortality Percentage *	Labile, Range in Mm. Hg	Mortality Percentage *
Systolic Averages			
0-5	206	6 or greater	224
0-10	194	11 or greater	226
0-12	202	12 or greater	255
0-15	211	16 or greater	237
Diastolic Averages			
0-5	193	6 or greater	221
0-8	200	9 or greater	222
0-12	210	13 or greater	185

* 100% mortality is representative of the substandard class to which the risk was assigned. From "Intercompany 1946-49 Select Mortality Table."

strable cardiovascular changes; disease of the renal, digestive, and nervous systems, or a history of these. The extreme upper levels of blood pressure were near the ranges of 180 mm. Hg systolic and 110 mm. Hg diastolic, these being the highest ranges in persons on whom insurance was issued. The subjects were all men because the number of women that could have been included was too small to be significant. The material for analysis was obtained from information in 2,510 life insurance policy files compiled between the years 1942 and 1954.*

The vitally important procedure by which the final blood pressure figures were obtained and used for risk evaluation is described below. It is assumed that all blood pressure readings were obtained with the subject in the seated position.

If the first current reading was elevated to a degree requiring an additional premium charge, according to tables based on combined company experience, a second reading was obtained and the average of these used.

If the variation between the two current readings (lability) was over 20 mm. Hg systolic or 10 mm. Hg diastolic, a third was obtained, the average of the three being used.

A prior reading (highest systolic and highest diastolic from any authentic source) was averaged with the required current readings if the average was thereby increased.

* Part of this statistical material was presented at the annual meeting of the Association of Life Insurance Medical Directors of America, Oct. 24, 1957. Reproduced by courtesy of the editor of "Transactions of the Association of Life Insurance Medical Directors of America."

Lability of Blood Pressure

In evaluating the factor of lability, the records from which the material was taken were restricted to those in which blood pressure observations were all made within a period of six months. The highest and lowest systolic and the highest and lowest diastolic pressures were accepted as the range of blood pressure (lability) for that person. Any bizarre variation in multiple readings would obviously introduce some distortion when the material was analyzed. This was avoided by further selecting for study only records in which the average systolic variation was within 5 mm. Hg of that average systolic pressure used for classification of the life insurance risk. The same limit of variability was also applied to the diastolic variations.

The data were then separated into groups for comparison of the long-range effect or mortality experience according to ranges of lability. The moderately increased mortality for each group was computed, and the results are listed in Table 1. In those persons with elevated *systolic* pressure there was no important variation between the mortality ratio of 237% for the division with labile characteristics and 211% for that with stable blood pressure. Likewise, it is apparent that in those with elevated *diastolic* blood pressure there was no significant difference in the mortality between the groups, 210% for the labile and 185% for the nonlabile.

When the groups were subdivided into lower ranges of variation, the results, listed in Table 2, again failed to reveal any important differences in the mortality experience between the labile and stable groups.

Life Expectancy

Life expectancy was determined by the usual method of comparison with the most recent commonly used standard, which is the "Intercompany 1946-49 Select Mortality Table." For convenience, the material was classified into age groups of 30-49 years (average of 40 being used) and 50 years and over (average of 55 being used). A

TABLE 3.—*Mortality Experience and Life Expectancy According to Blood Pressure Averages (Combined Nonlabile and Labile) 2,510 Subjects*

Entry Age	Mortality Percentage Group *		Life Expectancy, Yr.	
	40 Yr. Group	55 Yr. Group	40 Yr. Group	55 Yr. Group
Unimpaired risks	100	100	33.1	21.5
Systolic (mm. Hg)				
Below 150	288	155	23.0	18.3
150-159	362	254	22.0	14.7
160 or above	460	307	19.9	13.5
Diastolic (mm. Hg)				
Below 89	180	266	27.7	14.1
90 or above	391	234	20.9	15.5

* From "Intercompany 1946-49 Select Mortality Table."

quarter of the total number of cases, those entering the study under age 30, did not furnish a sufficient number of deaths for valid statistical analysis.

In the 40-year age group there was significant reduction in the life expectancy by nearly seven years (Table 3) when the *diastolic* pressure was 90 mm. Hg or higher, as compared to the lower levels. It is interesting to observe that this was not evident among persons in the older age group. In both age groups *systolic* blood pressure elevation was associated with a gradual slight decrease in life expectancy roughly in proportion to the pressure increase.

There were 120 deaths (Table 4) among the 2,510 policy-lives, representing a death rate of nearly 5% occurring between the years 1942 and 1954. It should be emphasized that none of the persons on whom data were obtained had severe degrees of arterial hypertension, these being rigidly excluded by the process of life insurance risk selection. It is interesting to note the

TABLE 4.—*Deaths in Age Groups* *

Entry Age	No. Deaths.	%
Under 30	4	3.6
30-49	67	55.6
50 & over	49	40.8

* The 120 deaths represented 4.78% of the 2,510 cases.

age distribution of those who died, 55% being in the 30- to 49-year group. This was compared to the distribution of deaths among policyholders of similar age groups who were issued insurance at standard premium rates, and the proportions were found to be the same in the two types of policyholders. No explanation is known for this coincidence.

Cause of Death

Death from the various cardiovascular-renal degenerative conditions might be expected to increase in frequency out of proportion to all other causes in persons with the background of mild or moderate hypertension. However, this is not apparent in the series studied. On the contrary, there is (Table 5) a close approximation of the percentages in these

TABLE 5.—*Distribution of Deaths by Cause*

Cause of Death	No. Deaths This Study,	Total Deaths, %	
		Metropolitan Life Insurance Co. *	This Study
Accidental death	5		4.2
Cerebrovascular lesions	13	10	10.9
Coronary artery disease	69	51	57.5
Malignancy	11	9	9.0
Malignant hypertension	4	2	3.3
Suicide	3	4	2.6
Other causes (not related to cardiovascular disease)	15		12.5
Total	120		100.0

* Deaths in white males, ages 20 years and over, during the year 1954, from the Industrial Premium-Paying policies of the Metropolitan Life Insurance Company of New York.

groups when compared to published data on causes of death in persons representing approximately the general male population. The incidence of coronary artery disease was only slightly higher in the groups reported on here. This was true also for those who developed malignant hypertension after being issued insurance, although the percentage for cerebrovascular lesions was nearly the same.

Conclusions

Among a highly selected group of persons with mild or moderate arterial hypertension, but otherwise in good health, there is no evidence that *lability* of the blood pressure was a significant factor in the moderately increased mortality experienced. Thus, the observed fluctuations in blood pressure did not indicate that the life span in these persons would be greater than that of persons with constantly observed hypertension. Therefore, it would seem proper to include a proportionate number of elevated readings with normal ones in the determination of the average blood pressure for an individual person.

These data also support the generally accepted conclusion that the significance of hypertension becomes less important as the age of the person advances.

Finally, the results of this study suggest the desirability for early recognition of temporary elevations in blood pressure and their importance to otherwise healthy persons.

The Mutual Life Insurance Company of New York, 1740 Broadway (19).

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Hemophilia B (PTC Deficiency, or Christmas Disease)

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In 1947, it was shown by means of a new procedure, the prothrombin consumption test, that blood did not contain thromboplastin either free or in a precursor state but that it was formed as the result of an interaction between a platelet factor and what was assumed to be at that time a single plasma constituent which was lacking in hemophilia.[1] Five years later Schulman and Smith[2] reported a patient whose clinical condition was indistinguishable from hemophilia but whose defective prothrombin-consumption time was corrected by plasma from a known hemophiliac. They concluded that their patient lacked a plasma factor different from thromboplastinogen, the agent deficient in hemophilia, but which was equally as essential for the formation of plasma thromboplastin. No specific name other than X was given to this new factor. Interestingly, a week after Schulman and Smith sent their manuscript for publication, Aggeler and his associates[3] submitted their report of a similar type of case. They observed that the new factor, which they designated as plasma thromboplastin component (PTC) was present in the serum as well as in the plasmas and, furthermore, that it was adsorbed by barium sulfate. This finding greatly assisted in the differential diagnosis, because the constitutent lacking in true hemophilia is not removed by adsorbents.

Shortly thereafter, Biggs and her coworkers[4] reported seven cases that presented the clinical picture of hemophilia but whose clotting time was corrected with hemophilic plasma. They applied their newly developed thromboplastin generation test[5] and found that the clotting defect in these patients was in the serum. Two of their patients were first cousins, and the family tree clearly suggested the same hereditary pattern as of true hemophilia, namely, that of a sex-linked recessive. They named the condition "Christmas disease," after the family name of their first patient. Soulier and Larrieu[6] somewhat later proposed the name hemophilia B for this new type of hemophilia, which name was adopted by others,[7] while Fantl and Sawers[8] called it β-prothromboplastin deficiency.

Although the existence of types of hemophilia different from the classical was suspected[9,10] because the clotting time of some patients was corrected by mixing their blood with that of presumably true hemophiliacs, this evidence was insufficient to establish with certainty a new hemophilic entity. The ease with which the thromboplastin-generation test differentiates true hemophilia from the newly discovered disease has made this test the choice in various clinics.[11-15] Rosenthal[16] applied the prothrombin-consumption test for differential diagnosis and modified the procedure by adding to the blood to be studied various agents, such as normal plasma, adsorbed plasma, and serum. Interestingly, the addition of normal serum brought about a good correction of the prothrombin consumption of a patient with PTC deficiency, but, oddly, this finding received no comment in the

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The name hemophilia B has been used because the disease is clinically and genetically very similar to classical hemophilia. PTC (plasma thromboplastin component) deficiency is the term used to denote the activity in normal serum, and thromboplastinogen, to indicate the factor lacking in classical hemophilia.

discussion and has received little attention subsequently.

The development and perfection of several laboratory tests in our laboratory for studying and differentiating the hemophilic group of diseases [17,18] has made it possible to attempt a rather extensive investigation of hemophilia B, or PTC deficiency. The opportunity to study 24 patients with this disease and the cooperation of several in this group to furnish blood and to serve as experimental subjects greatly facilitated the investigation.

Methods

Blood obtained by venipuncture with silicone-coated syringe and needle was immediately transferred to test tubes coated with silicone. These were kept in an ice bath. All tests were carried out in standard glass test tubes (13×100 mm.) at 37 C. Native platelet-poor plasma was obtained by centrifuging blood in a Superspeed Serval Centrifuge at 8,000 rpm for 20 minutes. This operation was carried out in a cold room (4 C). Most procedures employed in this study have been described previously [19]; therefore, only a brief outline of the various tests will be given.

Prothrombin-Consumption Time — Basic. — One milliliter of blood is transferred to a test tube and the clotting time determined at 37 C. Fifteen minutes after a solid clot has formed, the tube is centrifuged for one minute in a Clinical Centrifuge at top speed, which is approximately 2,000 rpm. The tube is again placed in the water bath for 45 minutes. The prothrombin activity of the serum is determined by accurately timing the clotting when 0.1 ml. is rapidly blown into the following mixture: 0.1 ml. of thromboplastin reagent (acetone dehydrated rabbit plasma), 0.1 ml. of deprothrombinized rabbit plasma, and 0.1 ml. of 0.02 M $CaCl_2$. The deprothrombinized rabbit plasma supplies fibrinogen and excess labile factor. A prothrombin time of eight to nine seconds is obtained when the consumption of prothrombin is very low, as in severe hemophilia, and when normal platelet-poor plasma is clotted.

TAT Test (Thromboplastinogen Activity Time): When an extract of rabbit brain is heated to 60 C for 20 minutes, it loses its holothromboplastic activity, since it no longer causes prothrombin consumption when added to hemophilic blood but retains an activity very similar to that of platelets. The test is carried out exactly as the basic prothrombin-consumption time, except that 0.05 ml. of the heated thromboplastin reagent is mixed with 1.0 ml. of the blood before clotting.

Hemolysate Test.—An extract of human erythrocytes contains an activity similar to platelets but of a much higher degree of potency. Other than mixing 0.1 ml. of the extract of hemolyzed erythrocytes with 1 ml. of blood, the test is identical with the basic prothrombin-consumption time.

Serum Correction Time Test.—The reagent is prepared by incubating the serum for one hour at 37 C after the blood has clotted and been centrifuged. It is then stored at 4 C for 24 hours. Several sera are pooled and kept at —20 C. The test is carried out as follows: 0.025 ml. of the aged serum is mixed with 1 ml. of blood. From this point, the procedure is the same as the basic prothrombin time.

Thromboplastinogen Assay.—The method of Quick [17] was employed. To 1 ml. of platelet-poor plasma from a severe case of true hemophilia, 0.1 ml. of hemolysate, 0.03 ml. of aged normal serum, and varying amounts (0.005 to 0.1 ml.) of the plasma to be assayed are added. The prothrombin-consumption time of the mixture is determined as in the basic prothrombin-consumption test. For normal persons, the addition of 0.005 ml. of plasma will yield a prothrombin-consumption time of about 30 seconds. A range of 15 to 35 seconds may be regarded as normal.

Thromboplastin-Generation Test.—The method of Biggs and Douglas [6] modified by using the platelet substitute described by Bell and Alton [20] was used.

Report of Cases

In Table 1 a summary of the laboratory studies and the important clinical findings of 24 cases are reported. Of these, several have been selected as representative of the group.

Case 1.—A boy was born in 1932. Easy bruising was noticed early. At the age of 3 years he bled severely from a cut on his lip. On losing temporary teeth, he bled so severely that two transfusions were given. At the age of 10 he was hospitalized eight times for nosebleeds. He had frequent involvement of his ankles, and he also had hemarthroses of other joints but suffered no permanent ankyloses. Two days after a fall with a presumable head injury he had convulsions but made a complete recovery. He missed much schooling during childhood, but his activities were not restricted. As he became older, his bleeding tendency lessened. He played baseball and tennis. Although he continued to have bleeding into his joints, nearly complete recovery of function has always returned. For the past 10 years he has had no epistaxes. Although he has an occasional hemorrhage into his joints and muscles, he has required no hospitalization since he was a child. He had few absences due

TABLE 1.—*Principle Laboratory and Clinical Findings*

	Case										
Birth Year	1 (1932)	2 (1914)	3 (1927)	4 (1956)	5 (1927)	6 (1942)	7 (1952)	8 (1950)	9 (1950)	10 (1942)	11 (1930)
Laboratory Findings											
Clotting time, min.	50	57	78	110	55	60	35	27	25	22	26
Prothrombin consumption time, sec.											
Basic	11½	12	11	12½	10	12	10	13½	14	14	13½
With TAT reagent	10	10	12½	12	10	10	10	13	12½	13½	13½
With hemolysate	15	11	15	13	14	16		16	15	19	15
With serum	19	18	19	23	31	16	23	28	33	41	26
With hemolysate & serum	48	70	66	37				132	110	61	
Thromboplastin generation test, sec.											
Plasma	8	9		..	7		7	8	8	10	9
Serum	36	24		44	26		22	30	31		31
Thromboplastinogen assay, sec.	27	27						23	32	26	11
Clinical findings											
Heredity	—	+	+	+	—	—	—	—	—	—	—
Hemarthrosis	+	+	+	—	+	+	+	+	+	+	+
Epistaxis	+	—	—	—	—	±	—	+	+	+	+
Hematuria	—	+	+	—	+	+	—	—	—	+	+
Transfusion	10+	10+	10+	1	10+	10+	10+	10+	10+	10+	10+

* Results of the prothrombin time, tourniquet, and bleeding time tests were within the normal range except in Case 18, who had
† Died of gastric hemorrhage.

to illness during high school and college, and he is now employed as a chemical engineer. On repeated studies, the clotting time has been found to be almost always 50 minutes or longer.

CASE 2 (Fig. 1, *II-1*).—A boy was born in 1914. During childhood he had numerous hemorrhages into his ankles, knees, and elbows. He developed a large hematoma after the suturing of a laceration above his right eye. He was unconscious for a week after a fall. Despite his bleeding difficulties, he was fairly active in sports. He became a factory worker and operated a drill press and also a punch press. Because of the hazards of this type of job, he had many injuries. After he was shifted to inspection work, his bleeding episodes decreased. Although motion in both knees and elbows is limited, function has remained good, and he continues in his employment. He has had frequent hematuria, which he attributes in part to acetylsalicylic acid. Since he has avoided this drug, the frequency of attacks has markedly diminished. He has bled from tooth extractions but no transfusions were required. He bled profusely after the removal of a nasal polyp. No benefit was obtained from a transfusion of banked plasma, but bleeding became controlled after banked whole blood.

CASE 3 (Fig. 1, *II-6*).—A brother of Case 2 was born in 1927. His first severe bleeding resulted from a myringotomy. At the age of 10 years he had 15 transfusions to control bleeding after the extraction of a tooth. He also received several transfusions for nosebleeds, but lately epistaxes have become infrequent. He has had somewhat fewer joint hemorrhages than his brother, and they began later in life. He has had several attacks of hematuria, but these usually stopped without treatment and did not keep him from work. Like his brother, he has noticed that acetylsalicylic acid increases his bleeding tendency and has observed petechiae after taking the drug. Although he has partial ankylosis of his knees and elbows, he continues his work as a paint sprayer with fairly little trouble. He was in military service for four months.

CASE 4 (Fig. 1, *III-10*).—A nephew of Cases 2 and 3 was born in 1956. He bled after circumcision, but local treatment controlled it. Easy bruising was observed early. When one year old, he had a laceration of his upper lip, a large ecchymotic swelling which closed his right eye, oozing from his gums, and a drop of hemoglobin to 6 gm.—all the result of a fall. He improved rapidly after a transfusion of fresh-frozen plasma and cell mass. At 1½ years he had tarry stools which cleared spontaneously. Bleeding from a small cut of the frenum responded promptly to a transfusion of 250 ml. of fresh-frozen plasma. As was true for his two uncles, his clotting time is about one hour or longer.

The mother of Cases 2 and 3 had two brothers in Poland who were severe bleeders and also a maternal uncle who had the disease.

CASE 8.—This boy was born in 1950. Early bruising was observed when he was 10 months old. His first admission to a hospital was when he was a little over one year old; he bled from a cut on his lip. He has had 115 hospital admissions and about 250 transfusions. Bruises, intramuscular bleeding, and epistaxes are his main types of hemorrhage. He has had hemorrhages into both ankles, but no other joints have been involved.

in Twenty-Four Patients with Hemophilia B*

(Year)												
12 (1938)	13 (1943)	14 (1954)	15 (1949)	16 (1947)	17 (1920)	18 (1881)	19 (1949)	20 (1932)	21 (1947)	22 (1945)	23 (1953)	24 (1934)
20	18	24½	17	14	12	14	9	11	11½	12½	11	10
12½	14	13	8½	12	11	15	14	13½	13½	13	14	27
12	11	12	11	10½	12	13	12	10	15	12	10½	9½
31	18	31	31	17	50	16½	38	31	41	12½	55	28
24	19	24	18		17	24	39	17	29	22	13	20
120	90				73			91	72			
		17	8	9	8	9½	10½		10	11	9	7
		28	31	24	21	35	38	34	14	21	40	12
		24		30	22						23	29
−	−	−	−	+	−	+	+	+	+	+	+	−
+	+	+	+	+	−	+	−	−	−	−	−	−
+	−	−	−	+	+	+	+	−	−	−	−	+
+	+	−	+	−	+	+	−	+	−	−	−	−
7	10+	4	10+	10+	0	3	1	0	5	5	0	5

a bleeding time of 9 min.

CASE 9.—This boy is a twin brother of Case 8 (fraternal). His history is similar to his brother, except that he has had more internal bleeding. At 5 years of age, he was operated on for acute appendicitis, but it was found that he had internal bleeding. He had severe postoperative bleeding. He, too, has had considerable trouble with bleeding into his ankles, and he has had hemarthrosis of one elbow.

A diagnosis of hemophilia was made when they were 2 years old. Both have been given commercial antihemophilic globulin. They have one normal brother. The family history is entirely negative.

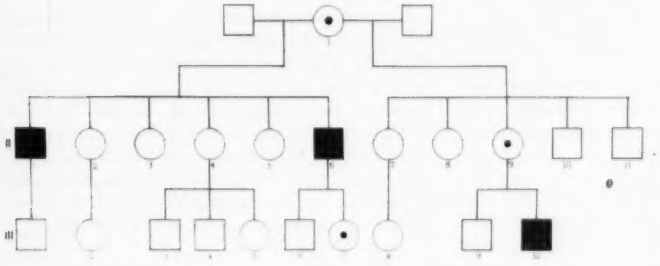

Fig. 1.—Pedigree of hemophilia B. All affected members of the family are severe bleeders. The carrier *I-1* had two brothers who were bleeders.

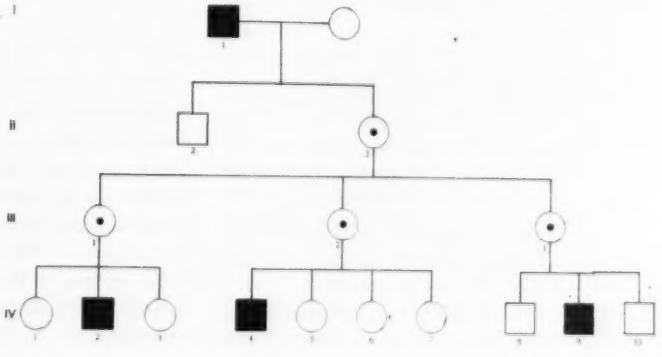

Fig. 2.—Pedigree of hemophilia B. The affected members of this family are mild bleeders.

CASE 22 (Fig. 2, *IV-2*).—This boy was born in 1945. He bled for five days after circumcision. At age of 1½ years, he bled for two weeks from biting his tongue. This happened again later. After this he had no serious bleeding but continued to bruise easily. At the age of 8 years he had a tooth extracted; to control bleeding two transfusions had to be given. In 1955, he had massive bleeding into his thigh. Heat was applied, which accentuated the bleeding. Complete paralysis of the leg occurred. On the fourth day he had an elevated temperature. Recovery, however, was rapid, and in two weeks he was able to return to school. For the past three years, he has had no severe bleeding and bruising has been less frequent.

CASE 21 (Fig. 2, *IV-4*).—A cousin of Case 22 was born in 1947. He bled after circumcision, but control was effected by suturing. He did not bruise easily as a baby. At the age of 2½ years, he had a large hematoma on his forehead due to a blow. He had a second head injury when he was 4 years old. Bleeding from the gash was controlled by pressure but recurred five days later when the bandage was removed; it was controlled by pressure and a suture. A third head injury a year later resulted in a large hematoma on his scalp. He complained of nausea and headache which persisted for a week; a roentgen examination showed no skull fracture. In 1955, he fractured his forearm. The fracture was reduced and the arm put in a cast. After three weeks, he began to complain of pain. On removal of the cast, it was found that no union of the bone had occurred and that a Volkmann contracture of the fingers had developed. Orthopedic treatment was instituted by Dr. Walter P. Blount after a transfusion of fresh-frozen plasma. Movement of the fingers gradually came back, but full function of the hand did not return until nine months later. In March, 1956, he had two teeth extracted. Six transfusions were required before bleeding was controlled. He had bleeding into his knee, which was successfully controlled by the application of ice; recovery was complete in six days. He has been well for the past two years except for easy bruising. He has no joint deformities.

CASE 23 (Fig. 2, *IV-9*).—This boy was born in 1953. Although his laboratory findings were abnormal, particularly the prothrombin-consumption time and TAT test when studied in 1955, no history of abnormal bleeding was obtainable. He was seen again recently when he had a hemorrhage above his left ankle with discoloration. Previously, he bled for a week after a minor cut of his lower lip. On examination a hematoma was found on his left forearm. His older brother is clinically normal. A younger brother has not been studied.

CASE 18.—This man was born in 1881 at Wallsenhausen, Switzerland. As a boy he had frequent epistaxes, bled from tooth extraction, and had deep intramuscular hemorrhages. In 1901, he went into military service. He had a leg injury causing a hematoma, which was incised. Severe bleeding resulted and this required 24 weeks of hospitalization at Basel. During this time he also had eight teeth extracted, which added to the problem of bleeding. He worked as a wagon maker until 1911, when he emigrated to America. He became a farmer and continued to work actively until 1954. In 1946, he had one transfusion for epistaxes and two in 1949 for the same type of bleeding. He had six attacks of hematuria and two gastrointestinal hemorrhages. The last kidney bleeding was 21 years ago. It is probable that he has had bleeding into his joints. Although flexion is limited to 90 degrees for both knees, it is not certain whether this has resulted from hemarthrosis or intramuscular bleeding. The elbows are limited in flexion and pronation. For the past few years bleeding has been mainly into the skin and muscles. He has had fewer bleeding episodes since he retired from active work. Interestingly, he has received only three transfusions in his 77 years.

He did not know of any bleeding in his family, but in the recent comprehensive study of the Tenna family by Moor-Jankowski and his associates,[21] this man was traced as a descendant. His mother was born near Tenna. He has two sons who are normal, and their children are normal. His daughter has one daughter who does not bleed and one son whose history follows.

CASE 19.—The grandson of Case 18 was born in 1949. He developed a large scalp hematoma at birth; he was given one transfusion. At the age of one year he had a hematoma of his cheek. Later, he had a hematoma of his leg. He occasionally has nosebleeds caused by hay fever, but these have not been serious. He has also bled from tooth extraction. He has received no transfusion except for the one immediately after birth, and he has not required hospitalization for bleeding.

Basic Defect

In hemophilia B, the clotting time is prolonged in all but the very mild cases, the one-stage prothrombin time is normal, the prothrombin consumption and utilization when measured either by the procedure of Quick[2] or of Brinkhous[3] are defective, and the thromboplastin generation as determined by the method of Biggs and Douglas[4] is poor. The defect has been localized in the serum by the latter test. From these findings, it has been generally accepted that hemophilia B is caused by the lack of a

specific clotting factor which is required for the formation of intrinsic or plasma thromboplastin. Because normal serum contains a high amount of the clotting agent, it has been generally accepted that the factor is not consumed during coagulation. The normal prothrombin time indicates that the components of the prothrombin complex, including prothrombin and labile (V) and stable (VII) factors, are present in normal concentrations.

A new means for studying the hemophilic group of diseases became available with the discovery of the new and potent clotting factor in erythrocytes[22] designated as "erythrocytin."[23] In the test tube, this agent fully replaces platelets in the clotting reaction; in fact, it is far more potent. When an extract of erythrocytes is added to normal platelet-poor plasma, a high consumption of prothrombin results, as shown in Table 2. It is, however, very ineffective

TABLE 2.—*Differentiation of Hemophilia B from True Hemophilia by the Prothrombin-Consumption Test, with Use of Hemolysate, Normal Aged Serum, and Plasma*

		Prothrombin Consumption Time, Sec.		
	Ml.	Normal	True Hemophilia	Hemophilia B
Native platelet-poor plasma	1.0	8	8	11
With				
Hemolysate	0.1	55	8	11
Serum, aged normal	0.03	8½	8	11
Hemolysate	0.1	135	8	70
Serum	0.03			
Hemolysate	0.1	55	30	11 *
Fresh normal plasma	0.005			

* Even 0.1 ml. of plasma did not increase the prothrombin consumption.

when added to either hemophilia or hemophilia B plasma, because these lack factors with which it presumably reacts to form thromboplastin. Aged serum alone, when added to platelet-poor plasma, is without effect, since it does not supply either the platelet factor or a functioning platelet substitute. When both hemolysate and serum are added to hemophilia B plasma, the consumption of prothrombin is markedly increased. The simple explanation is that normal serum supplies the factor lacking in hemophilia B and that hemolysate furnishes the second essential component, while the third, namely, thromboplastinogen, is present in normal concentration in hemophilia B plasma, as is shown by the results in Table 1.

Significantly, the addition of normal plasma and hemolysate to hemophilia B plasma does not cause any measurable increase in the consumption of prothrombin, such as occurs in the plasma of a true hemophiliac. It is obvious that the factor which is abundantly present in aged normal serum is absent in fresh normal plasma. Yet, plasma must be the source of the serum factor. The most obvious explanation is that the factor is present in normal plasma in an inactive or precursor state. Before it can function in the generation of thromboplastin, the agent must be activated. This occurs normally during coagulation. Thus, on adding hemolysate to normal human platelet-poor plasma, the activation of the factor proceeds rapidly enough during clotting to cause a high consumption of prothrombin. When hemolysate is added to platelet-poor rabbit plasma, poor consumption occurs.[24] The most probable reason is that the activation of the factor is too slow to allow it to enter into the terminal reaction that generates thromboplastin. It would be easy to misinterpret this observation to mean that rabbit plasma lacks PTC, but the finding that rabbit serum contains the active principle shows that the defect is in the activation. Since the experiment on platelet-poor rabbit plasma was carried out in glass, it is not lack of contact with a foreign surface that accounts for failure of inactivation, as has been postulated.[25,26] The determination of PTC activity in serum may not necessarily always be a true measure of its concentration in plasma, since faulty activation can also account for a low concentration of the active factor. Bergsagel[27] recently postulated that PTC in serum exists in a complex with calcium,

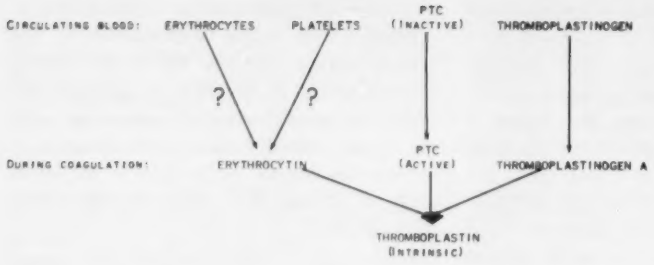

Fig. 3.—The probable mechanism for the formation of plasma or intrinsic thromboplastin. The origin of erythrocytin is still uncertain. It is probable that both PTC and thromboplastinogen may require activation before their interaction with erythrocytin.

whereas in plasma it is not associated with calcium.

Intrinsic or plasma thromboplastin is apparently formed from three immediate agents: erythrocytin, the serum factor commonly called PTC, and thromboplastinogen. How erythrocytin is formed is not known, but it seems probable that a platelet agent is its precursor and that its presence in erythrocytes is merely coincidental. In the presence of excess erythrocytin, the consumption of prothrombin depends on the amount of activated PTC and the quantity of thromboplastinogen. Erythrocytin, therefore, probably becomes the most reliable agent for assaying these two plasma factors. A probable scheme of formation of intrinsic thromboplastin is given in Figure 3.

Diagnosis

Prior to 1952, classical hemophilia was not differentiated from hemophilia B. Much of the accumulated data, therefore, are of doubtful value and require judicious care in evaluation. The bleeders of the well-known family of Tenna were regarded as true hemophiliacs, but it is now known that the disease in this family is hemophilia B.[28] Two descendants are included in the 24 cases reported in this paper. Apparently, it has not been determined which type of hemophilia was transmitted by Queen Victoria.

The diagnosis of hemophilia B, like that of the classical disease, depends on the triad of a bleeding state manifesting itself early in life, a characteristic hereditary pattern, and definitive laboratory findings. As in true hemophilia, a positive hereditary history of a sex-linked recessive is obtainable in only about one-half of the cases. When heredity can be established, the reliability of the diagnosis is enhanced.

The diagnosis of hemophilia B is not difficult and can be made with a few relatively simple laboratory procedures of which the prothrombin consumption time and its three modifications, namely, the TAT, hemolysate, and serum tests, have been found to be the most valuable and trustworthy. The results presented in Table 3 clearly show the similarities and differences between true hemophilia and hemophilia B and indicate how the two diseases can be differentiated. It is important to note that the defective prothrombin consumption in hemophilia B is corrected by adding aged normal serum to the blood before it is clotted. Serum does not correct the faulty consumption of prothrombin of hemophilic blood.

It is interesting to note that in true hemophilia the prothrombin-consumption time, especially with the hemolysate test, is almost directly related to the clotting time. When the clotting time is above 25 minutes, little consumption of prothrombin occurs, but as the value decreases from 25 minutes to normal, the consumption time as measured by the hemolysate test becomes greatly increased. While the basic prothrombin-consumption time and the TAT test yield low values in hemophilia B, the times are not as short as in true hemophilia, and the correlation with the clotting time is not as definite.

TABLE 3.—*Differentiation of Hemophilia B from True Hemophilia by the Prothrombin-Consumption Tests* *

	Clotting Time, Min.	Prothrombin Consumption Time, Sec.			
		Basic	TAT	Hemolysate	Serum
Hemophilia					
Case 25	60	8	8	9	8
Case 26	80	9	9	9	9½
Case 27	83	9	9½	9	9½
Case 28	25	9	9	19	9
Case 29	11	12	10	25	11
Hemophilia B					
Case 3	78	11	12½	15	19
Case 30	55	10	10	14	31
Case 8	27	13½	13	16	28
Case 9	25	14	13½	15	33
Case 19	9	14	12	38	39

* Cases 26 and 27 are identical (enzygotic) twins; Cases 8 and 9 are fraternal (dizygotic) twins.

It is clear from the five cases selected for illustration in Table 3 that the battery of consumption tests is sufficient to make the diagnosis of hemophilia B with certainty, whether the case is mild or severe. If further diagnostic data are required, the prothrombin-consumption test on native platelet-poor plasma, as shown in Table 2, can be employed. Hemophilia B plasma will show no significant increase in prothrombin consumption on the addition of either hemolysate or serum alone, but when the two reagents are added together, an exceedingly high consumption of prothrombin is effected. This finding establishes the diagnosis with a high degree of certainty.

The prothrombin time in hemophilia B is normal, as it is in the classical disease. With this finding, hemophilia B is readily differentiated from the various hypoprothrombinemic states, including labile-, stable-, and Stuart-Prower-factor deficiencies.[29-31] The bleeding time, likewise, is normal, but occasionally in both true hemophilia and hemophilia B a temporarily prolonged bleeding time may be observed. The writers have found this in several of their authentic classical hemophiliacs. In this series a descendant of the family of Tenna had a bleeding time of nine minutes, while that of his grandson, who also is a bleeder, was normal. Combrisson-Le Bolloch,[32] Soulier and Larrieu,[33] Sjølin and Videbæk,[34] and Achenbach and Klesper[35] have reported prolonged bleeding times with PTC or Factor IX deficiency. Whether such cases represent a new clinical entity similar to pseudohemophilia B or, as it has been called by some, vascular hemophilia, remains to be determined.

The thromboplastin-generation test is very useful for differentiating classical hemophilia from hemophilia B. Serum from a patient with the latter disease is markedly deficient in PTC activity, but adsorbed plasma from such a patient has normal thromboplastinogen activity. Consistently good results with the test were obtained on all the cases of this series (Table 1). The method, however, has one serious shortcoming: It is not quantitative and does not distinguish between severe and mild bleeders. Even more disconcerting, a carrier may have values as abnormal as a bleeder, and occasionally the son of a carrier who has no bleeding tendency may show as low results as a true bleeder. The findings obtained on various members of an affected family are given in Table 4. The mother and her one son have no bleeding tendency, and the results of the prothrombin-consumption tests are normal; yet, their sera as measured by the thromboplastin-generation test are as abnormal as those of a known bleeder. Biggs and Macfarlane[36] have also observed that some females of hemophilia B families have abnormal thromboplastin-generation tests. Didisheim et al.[37] have also reported that 4 of 14 carriers of hemophilia B whom they studied had defective thromboplastin-generation tests.

While the thromboplastin-generation test clearly differentiates between true hemophilia and hemophilia B, it should not be the only test employed for diagnosis. In our laboratory the battery of prothrombin-consumption tests has been found to be most reliable in identifying bleeders and in estimating the severity of the coagulation defect.

TABLE 4.—*Thromboplastin-Generation Test Applied to Family with Hemophilia B*

	Case					
	32 *	33 *	34 *	23 †	31 †	17 ‡
Thromboplastin generation test, sec.						
Plasma	9, 9 §	9, 9, 8 §	9	9	8	8
Serum	12, 10 §	11, 14, 11 §	17	40	21	21
Clotting time, min.	7	6½	7	8	6	8½
Prothrombin consumption time, sec.						
Basic	20	30	21	14	23	13
With TAT reagent	23	42	25	10½	17½	11
With hemolysate	109	91	80	55	96	73
With serum	19	31	23	13	23	20

* Each one of these three sisters, whose father was a bleeder, has one son with hemophilia B.
† Cases 23 and 31 are the sons of Case 34; only Case 23 has a history of bleeding.
‡ Case 17, who is unrelated to the family, has mild hemophilia B.
§ Results were obtained at different times.

The typical case of hemophilia B offers no difficulty for diagnosis. The results of either the prothrombin-consumption test or the thromboplastin-generation test can differentiate the disease from hemophilia. It is the occasional isolated case which can present difficulty. Thus, the patient who is a descendant of the family of Tenna was found to have a prolonged bleeding time. If his hereditary history were not known, and if he did not have a grandson with typical hemophilia B, one could easily make the mistake of diagnosing him as having vascular hemophilia B.

It is particularly difficult to evaluate the reported cases in which the deficiency of PTC is accompanied by a lack of the antihemophilic factor.[30,39,40] Two of the cases reported had been studied previously in our laboratory and found to be classical hemophiliacs and later restudied by Dr. William F. Stapp, who confirmed our diagnosis and observed that their blood was not corrected by normal serum.

Heredity

The original observation of Biggs et al.[4] that hemophilia B, like the classical disease, is transmitted as a sex-linked recessive has been verified repeatedly.[41,42] We have had the opportunity to study two families in which the hereditary pattern is unmistakable. In the first pedigree (Fig. 1), the disease is severe, since all the affected members have a clotting time of one hour or longer. The carrier I-1 had two bleeder sons from her first husband. From her second, she had two normal sons and one established carrier who has one normal and one bleeder son. The laboratory findings and clinical histories of the two affected brothers and their nephew are similar, except that the nephew who is only 2 years old has had only two hospital admissions so far.

The second family, in marked contrast, represents a very mild bleeding state (Fig. 2). The first member to which the disease could be traced was apparently a mild bleeder. His daughter transmitted the defect to her three daughters, and each one has one bleeder son. The disease is so mild, however, that hemarthroses are either infrequent or absent and no permanent joint injuries have occurred. The three cousins have approximately the same laboratory findings, and their clinical course is different only in the number of accidents that they have had.

The two descendants of the Tenna family, grandfather (Case 18) and grandson (Case 19), also have a mild type of hemophilia B. The slight variation in laboratory findings can probably be accounted for by the difference in ages, 77 and 9 years. The mildness of the disease is attested to by the fact that the grandfather was gainfully employed past the age of 70 years, required

only three transfusions, and is still in good health.

These three families supply evidence that that the transmission of the defect in hemophilia B like that of classical hemophilia is quantitative. All affected members of a family have the deficiency to the same degree and have about the same clinical history. It is interesting to note that the two pairs of twins, one pair with true hemophilia and the other with hemophilia B (Table 3), illustrate the quantitative inheritance of the disease.

It is probable that hemophilia B can occur in a woman, provided the father is a bleeder and the mother is a carrier. A patient has been reported by Hardisty [43] whose father was a bleeder; she has bled only after tooth extraction. Since she has had no other types of bleeding, and the diagnosis was made exclusively on the serum abnormality with the thromboplastin generation test, there is still some uncertainty whether she is a true bleeder. Recently, we [31] reported a bleeding state in a girl whose laboratory findings are indistinguishable from true hemophilia but whose family history is negative. It is possible that a case of hemophilia B could occur under similar conditions.

One of the unexplainable observations is the lower incidence of hemophilia B as compared with the classical disease. In the recent survey of Biggs and Macfarlane,[36] they had 20 cases to 138 of classical hemophilia in their own series and, for the total number of cases reported in England, 29 to 220 of true hemophiliacs. Fantl and Sawers [8] had 6 to 37, and Frick [44] had 10 to 45. In the summary of cases by Ratnoff and Margolius,[45] the ratio of hemophilia to hemophilia B was 410:78; this summary includes the series of Rappaport.[46] During the period we studied the 24 patients reported in this paper, we diagnosed about 120 cases of true hemophilia. Since our patients come from a large area including both rural and urban population, the ratio of the two types of hemophilia can be regarded as fairly accurate.

It has been pointed out that hemophilia should eventually disappear by dilution,[47] and since it does not, new cases are best accounted for by mutation. If this is correct, then the mutation rate of hemophilia B must be regarded as being lower than that of true hemophilia.

Clinical Picture

Hemophilia B varies clinically from the very mild or almost subclinical to the very severe, as does the classical disease. In the mild case, bleeding may occur only after severe trauma or following a minor operation, such as tooth extraction. Hemarthroses are uncommon, and, when they do occur, are not apt to cause ankylosis, especially if properly treated. Even in the mild cases, the typical hematoma following contusions is common. Surprisingly, many of these children play roughly and engage in rather strenuous sports with impunity.

In the severer types, hemarthroses are the rule, and, in many, permanent joint deformities result. Deep intramuscular bleeding is fairly common. Bleeding occurs invariably following circumcision, tooth extraction, and other operations, unless the patient is treated prophylactically. Nearly all patients have hematuria before they complete the second decade of life; this form of bleeding seems somewhat more common than in true hemophilia. The incidence of epistaxis, likewise, appears to be higher than in the classical disease.

Clinically, hemophilia B even in its severe form appears to be less incapacitating than true hemophilia, especially after the person is past adolescence. The five adult subjects of this series with clotting times consistently about one hour or more are gainfully employed in industry and have long periods of freedom from serious bleeding. Even though in true hemophilia one occasionally encounters persons with clotting times of 50 to 70 minutes who do not require transfusions and hospitalizations for periods of years, they are in the minority. In both types of hemophilia, neurological complica-

tions are relatively infrequent, but they do occur. In one of the patients, convulsions developed after a head injury. Douglas and McAlpine [48] reported nerve compression as the result of bleeding in three patients and fatal cerebral bleeding in a fourth.

It has been found in our laboratory that the very mild classical hemophiliac has a normal clotting time, if the concentration of thromboplastinogen in his plasma is about 1%. When the clotting time is 25 minutes or longer, the concentration of thromboplastinogen is below 0.1%. The bleeding tendency, however, may be as severe in a bleeder with a clotting time of 15 minutes as in one with 45 minutes. Unfortunately, the lack of an accurate and delicate method to assay the concentration of the clotting factor lacking in hemophilia B does not make it possible to correlate the clotting time with the concentration of the specific clotting factor and the bleeding tendency. It seems justifiable, however, to postulate that a somewhat similar relationship holds.

Patients with either true hemophilia or hemophilia B who have a slightly prolonged clotting time almost always will bleed from a minor operation, such as the extraction of a tooth or circumcision, but they may not bruise abnormally from rather severe contusions. Often long periods of freedom from spontaneous bleeding are enjoyed, but suddenly a bleeding cycle may set in, when even such minor trauma as that caused by a hypodermic injection may cause a massive subcutaneous and intramuscular hemorrhage. This suggests that a vascular factor is superimposed on the basic clotting defect. Interestingly, several patients have noted a significant reduction in their bleeding episodes after they stopped taking acetylsalicylic acid. It is not uncommon to find that a bleeding cycle seems to be initiated by a cold or infection. The factors that maintain vascular tonus are still poorly understood, which makes the approach to the actual cause of the bleeding cycles difficult. Sufficient observations have been made, nevertheless, to suggest that hemostasis involves other mechanisms and reactions besides the generation of thrombin and the conversion of fibrinogen to fibrin.

Therapy

The treatment for true hemophilia, which has been outlined in the recent monograph,[19] has been found equally satisfactory for hemophilia B. The local and immediate treatment of injuries, particularly of the joints, by the application of cold and pressure has been found to be effective and beneficial, as in classical hemophilia.

For bleeding that cannot be controlled locally, a transfusion of fresh or fresh-frozen plasma has been found most satisfactory. Fresh whole blood has been given only when much blood has been lost externally or the hemoglobin has become alarmingly low. Since extravasated blood is eventually reabsorbed and the iron salvaged, repeated whole-blood transfusions will result in an excessive accumulation of iron.

In true hemophilia the effect of adding 1 part of normal plasma to 1,000 parts of the patient's plasma in vitro can be measured with precision [17] and the effect of a plasma transfusion can be determined with a similar high degree of accuracy by means of the prothrombin-consumption test and its three modifications. In hemophilia B the effect of a plasma or whole-blood transfusion also can be measured by these tests, as shown in Table 5. The results are not as definite. Aggeler [49] has stated that a reliable quantitative measurement of the PTC factor is lacking. The probable reason for this is that PTC is inactive in plasma and it is not known how it can be quantitatively activated. The results of the hemolysate test appear to be most helpful in estimating improvement of the clotting defect after transfusion.

In preparing an adult patient for tooth extraction, a transfusion of 500 ml. of fresh-frozen plasma has been found adequate. Fresh whole blood has not been found to have an advantage over plasma. Since serum corrects the defect of hemophilia in a test tube, it would appear to be

TABLE 5.—*Effect of Transfusion of Fresh-Frozen Plasma or Fresh Whole Blood in Hemophilia B*

	June 6 Transfusion 500 Ml. Plasma		June 9	June 11 Transfusion 500 Ml. Blood	
	Before	After		Before	After
Clotting time, min.	35	10	15	14	10
Prothrombin consumption time, sec.					
Basic	12	10½	11½	10	11½
With TAT	14	25	9	9½	10½
With hemolysate	19	29	25	9	22
With aged serum	18	21	15	13	40

the most satisfactory means for treating the disease, but Nour-Eldin and Wilkinson [50] have observed that a serum transfusion did not correct the clotting defect as measured by the thromboplastin generation test. Heni and Krauss [51] have had only partial success with serum in controlling bleeding after tooth extraction, and Brafield and Case [52] found that PTC activity decreased in plasma on storage. In view of these findings fresh or fresh-frozen plasma seems to be the most reliable agent at present. There has been no opportunity to test whether it will be as trustworthy for major surgery in patients with hemophilia B as we have found it to be in classical hemophilia.

Summary

A study of 24 cases of hemophilia B ranging from the severe to the very mild form confirms the reports of other investigators that the disease closely resembles classical hemophilia in its clinical manifestations and in its hereditary pattern. Both forms are transmitted as sex-linked recessives. The disease appears to be somewhat less severe and disabling than true hemophilia. The treatment for both diseases is the same. Fresh or fresh-frozen plasma has been found to be the most reliable agent to correct temporarily the coagulation defect. As in previously reported series, the ratio of hemophilia B to classical hemophilia is found to be approximately 1:5.

The factor which corrects the clotting defect of hemophilia B in a test tube is abundantly present in aged normal serum but is absent in normal plasma. This suggests that the factor lacking in hemophilia B is present in an inactive state in normal plasma. The consumption of prothrombin of native platelet-poor hemophilia B plasma is completely corrected by the addition of aged serum and an extract of erythrocytes, whereas true hemophilic plasma is not, which constitutes a basic means for differentiating the two diseases. The thromboplastin-generation test of Biggs and Douglas, likewise, is useful in the differential diagnosis of the two hemophilic states. It was not found possible to estimate PTC quantitatively.

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Interpretation of Symptoms with a Data-Processing Machine

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Recognizing that machines in the practice of medicine are here to stay, physicians have the obligation to learn as much of their advantages and limitations as they can comprehend. The machine described here merely correlates symptoms set down by the patient and draws conclusions on the basis of what it has "learned" from physicians. Hence it makes the same errors as the human brain which "taught" it plus others that are inherent in its inability to initiate the thinking process. One reviewer of the paper presented below asked this important question, "What is the character of the error when a diagnosis is made which is not correct? If a patient with flat feet is simply not so diagnosed, this is one type of error, but if the machine reads, 'respiratory tuberculosis inactive,' it's another." This and many other questions properly may arise.

At the same time, the device is an extremely ingenious one and does eliminate the factors of emotional bias and fatigue, which may confuse the issue when a physician tries to analyze the complex of subjective complaints which the patient serves up to him. Whether the machine described here will have a place in the internists' armamentarium cannot be determined until more of them know about it.

P. S. R.

The claim is frequently advanced that the process of drawing correct diagnostic inferences from a patient's symptoms is in large part indefinable and intuitive. It is the purpose of this communication to show that the making of correct diagnostic interpretations of symptoms can be a process in all aspects logical and so completely defined that it can be carried out by a machine.

The machine chosen for this demonstration is a conventional high-speed electronic data-processing system, programed to make diagnostic decisions in a manner analogous to that of an unbiased physician.[1]

First, the system ascertains valid diagnostic criteria for the diseases it studies. By relating symptoms to the diseases in which they occur, the system determines for each disease the symptoms that have diagnostic significance. This information is stored in the "memory" of the machine. To make a differential diagnosis, the machine system compares the symptoms of a patient to the syndromes in its memory, computes the likelihood of the patient having any of the diseases about which it possesses information, and identifies the disease syndromes which the person's symptoms most closely resemble. All these comparisons, computations, and decisions are completed within one second.

Statistical and mathematical details of the procedure are described elsewhere.[2] Presented here are data on the accuracy with which the machine makes diagnostic decisions, with comparisons to the accuracy of decisions made by a physician interpreting the same symptoms.

Method

The diagnostic significance of symptoms was determined and a statistical diagnostic method developed with data referring to 5,929 consecutive

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Copies of the Cornell Medical Index-Health Questionnaire may be obtained from the authors, The New York Hospital, 525 E. 68th St. (21).

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TABLE 1.—*Cases Diagnosed by Data-Processing Machine (Men)*

Diseases (1956 Sample)	Cases Examined, No.	Cases Correctly Diagnosed, %	Diseased Organ Systems Identified, %
Respiratory tuberculosis, active	2	0	0
Syphilis, latent	5	60	60
Dermatophytosis	27	7	22
Malignant neoplasm of stomach	2	50	100
Malignant neoplasm of lung	5	60	60
Nasal polyps	9	56	67
Benign neoplasm of skin	7	0	0
Lipoma	19	0	0
Diabetes mellitus	37	65	65
Obesity	46	78	78
Psychoneurosis	156	46	46
Epilepsy	5	100	100
Migraine	8	38	38
Cataract	28	21	25
Errors of refraction	50	14	32
Conjunctivitis	15	60	60
Otitis media	10	10	20
Deafness	17	53	59
Rheumatic mitral disease, inactive	11	55	73
Hypertensive cardiovascular disease	52	63	73
Diseases of coronary arteries	97	51	68
Functional diseases of heart	11	45	45
Arteriosclerosis	22	59	59
Varicose veins of lower extremities	80	71	74
Hemorrhoids	57	72	72
Phlebitis of lower extremities	6	67	83
Acute nasopharyngitis (common cold)	6	17	67
Tonsillitis	4	25	25
Chronic bronchitis	14	50	71
Sinusitis	37	49	62
Deflected nasal septum	60	37	53
Allergic rhinitis (hay fever)	14	14	86
Asthma	22	41	73
Pulmonary emphysema	65	31	38
Infected teeth & gums	53	2	2
Ulcer of duodenum	19	68	95
Inguinal hernia	109	71	71
Constipation	28	46	64
Functional gastrointestinal disorder	19	68	79
Irritable colon	28	25	64
Biliary calculi	16	50	88
Renal calculi	19	63	74
Cystitis	6	50	83
Stricture of urethra	3	33	33
Hypertrophy of prostate	134	40	55
Prostatitis	19	32	68
Hydrocele	8	25	50
Furuncle & carbuncle	13	46	54
Acne	53	15	30
Neurodermatitis	25	28	68
Eczema	12	58	75
Psoriasis	22	41	50
Dermatitis venenata	23	70	70
Rheumatoid arthritis	4	25	50
Osteoarthritis	36	69	69
Curvature of spine	9	0	11
Bursitis & synovitis	9	0	56
Pes planus	0	0	0
Respiratory tuberculosis, arrested	7	57	71
Syphilis, adequately treated	12	8	8
Total, 60 diseases	1,697	45	56

adult white patients (2,718 men and 3,211 women) admitted to the outpatient departments of The New York Hospital during the 18-month period beginning July 1, 1948. The method was tested with data referring to 2,745 consecutive adult white patients (1,280 men and 1,465 women) admitted during the 12-month period beginning Jan. 1, 1956.

Each patient's symptoms were elicited through a printed form, the Cornell Medical Index-Health Questionnaire (abbreviated CMI).[5] The CMI asks 195 questions about comprehensive medical history, and the patient responds to each of these by circling a "yes" or a "no." The questions, which are those usually asked in a detailed general medical interview, are concerned with a review of systems, past history of specific diseases, family history, and psychiatric complaints.

Additional data abstracted for analysis from hospital records include each patient's sex and age, along with the diagnoses made by hospital physicians after eliciting a history and performing physical and laboratory examinations. These diagnoses form the standard against which the accuracy of the machine is evaluated.

The 60 diseases most frequently diagnosed by hospital physicians in men of the 1948-1949 sample and the 60 diseases in women were chosen for study. These diseases are enumerated in Tables 1 and 2. Since more than one disease was diagnosed in some patients, the total number of diagnoses examined is greater than the number of patients.

From the CMIs of the 1948-1949 sample, the machine system determined the frequency with which patients having a given disease made each complaint and compared to it the frequency with which all patients in the sample made the same complaint. From these comparisons the machine derived the probable association between a specific complaint and a given disease.

It may be pointed out that the number of cases for comparison used in developing this method is unusually large for a medical investigation; there were from 10 to 100 times as many cases not diagnosed as having a given disease as there were cases of the disease.

TABLE 2.—*Cases Diagnosed by Data-Processing Machine (Women)*

Diseases (1956 Sample)	Cases Examined, No.	Cases Correctly Diagnosed, %	Diseased Organ Systems Identified, %
Dermatophytosis	13	8	38
Malignant neoplasm of breast	11	9	27
Fibroma of uterus	19	42	53
Polyps of genital organs	6	17	50
Benign neoplasm of skin	13	0	31
Diabetes mellitus	34	41	41
Nontoxic nodular goiter	38	47	50
Toxic diffuse goiter	20	15	35
Obesity	151	81	81
Psychoneurosis	293	31	31
Epilepsy	7	57	57
Migraine	7	28	28
Cataract	43	40	51
Errors of refraction	74	11	24
Conjunctivitis	15	60	73
Otitis media	17	82	94
Deafness	24	54	67
Rheumatic mitral disease, inactive	15	67	73
Hypertensive cardiovascular disease	41	78	78
Diseases of coronary arteries	59	51	66
Functional diseases of heart	11	9	55
Arteriosclerosis	11	73	73
Varicose veins of lower extremities	145	68	70
Hemorrhoids	60	77	77
Phlebitis of lower extremities	5	80	80
Acute nasopharyngitis (common cold)	1	0	0
Tonsillitis	2	0	0
Chronic bronchitis	9	44	44
Sinusitis	19	57	58
Deflected nasal septum	37	40	59
Allergic rhinitis (hay fever)	21	38	71
Asthma	15	33	47
Infected teeth & gums	49	0	0
Ulcer of duodenum	11	64	82
Constipation	54	50	69
Functional gastrointestinal disorder	13	46	69
Irritable colon	54	20	67
Biliary calculi	64	56	69
Pyelitis	6	50	83
Renal calculi	7	86	86
Cystitis	20	70	75
Cervicitis	78	0	29
Cystocele & rectocele	48	6	35
Malposition of genital organs	5	20	20
Menopause	17	53	59
Menstrual disorders	27	52	63
Benign cyst of breast	4	0	50
Furuncle & carbuncle	9	44	56
Acne	62	21	40
Neurodermatitis	41	61	66
Eczema	18	50	50
Urticaria	0	0	0
Psoriasis	19	47	63
Dermatitis venenata	68	49	63
Rheumatoid arthritis	9	11	89
Osteoarthritis	59	37	71
Curvature of spine	17	41	47
Bursitis & synovitis	13	0	38
Pes planus	2	50	50
Respiratory tuberculosis, arrested	9	56	56
Total, 60 diseases	2,029	43	54

From the probabilities attached to each complaint on CMIs of those in the 1948-1949 sample, the machine derived an average score for each disease and used these averages in interpreting the complaints of the patients in the 1956 sample. For the 1956 sample it computed a patient's score for each disease, corrected the score for age, and related the score to the average score obtained by the 1948-1949 patients who had that disease. On the basis of this relation, the machine assigned a likelihood index that a patient had any of the 60 diseases studied. When the likelihood index for any disease reached a certain level, it was taken that the machine had diagnosed the presence of that disease in the patient.

Results

The CMIs of all patients in the 1956 sample were interpreted by the machine. Table 1 lists for men and Table 2 for women the per cent of cases of each disease correctly identified by the machine method. Also given is the per cent of cases in which the machine correctly identified the organ system diseased.

These tables reveal that there is a wide variation among diseases in the per cent of cases correctly diagnosed by the machine method. In as many as 68% of cases the machine correctly identified diseases such as ulcer of the duodenum, about which the CMI elicits many symptoms. Of diseases about which the CMI elicits no pertinent information, such as benign neoplasm of the skin, it identified no cases at all.

The tables, in which data are summarized for the entire 1956 sample, show that the machine diagnosed correctly 44% of cases (45% in men and 43% in women) of the 60 diseases. The tables show also that the machine method correctly identified the

TABLE 3.—*Diseases Other Than Psychoneurosis Correctly Diagnosed by a Data-Processing Machine and by a Physician, Solely from Data on the CMI* *

Cases Diagnosed Correctly, %			
By Physician but Not by Machine	By Both Physician & Machine	By Machine but Not by Physician	By Neither Physician Nor Machine
Men †			
7	39	14	40
Women ‡			
13	28	15	44

* Based on 158 men and 192 women of the 1956 sample examined in the General Medical Department.

† % of all cases diagnosed correctly by the physician, 46%; by the machine, 53%. Difference between ability of the physician & of machine to diagnose cases correctly (critical ratio 1.59) statistically not significant.

‡ % of all cases diagnosed correctly by the physician, 41%; by the machine, 43%. Difference between ability of physician & of machine to diagnose cases correctly (critital ratio 0.45) statistically not significant.

organ system diseased in 55% of cases (56% in men and 54% in women) of the 60 diseases studied.

The machine and a physician experienced in the use of the CMI were compared in ability to diagnose the 60 diseases from CMI data exclusively. The CMIs of 350 patients selected at random, examined in the General Medical Department, were interpreted independently by the machine method and by the physician.

TABLE 4.—*Cases Correctly Diagnosed as Psychoneurotic by a Data-Processing Machine, and by a Physician, Solely from Data on the CMI* *

Cases Diagnosed Correctly, %			
By Physician but Not by Machine	By Both Physician & Machine	By Machine but Not by Physician	By Neither Physician Nor by Machine
Men †			
31	43	2	24
Women‡			
47	39	0	14

* Based on 158 men and 192 women of the 1956 sample examined in the General Medical Department.

† % of all cases diagnosed correctly by the physician, 74%; by the machine, 45%. Difference between ability of physician & of machine to diagnose cases correctly (critical ratio 2.71) statistically significant beyond the 0.01 level.

‡ % of all cases diagnosed correctly by the physician, 86%; by the machine, 39%. Difference between ability of physician & of machine to diagnose cases correctly (critical ratio 5.95) statistically significant beyond the 0.01 level.

These comparisons are given in Table 3 for all diseases except psychoneurosis and in Table 4 for psychoneurosis. Table 3 reveals that the physician correctly identified 43% of cases of diseases other than psychoneurosis (46% in men and 41% in women), while the machine correctly identified 48% (53% in men and 43% in women). Statistically, the physician and the machine did not differ significantly in their ability to identify correctly these diseases from CMI data.

For psychoneurosis (Table 4), the physician is clearly superior to the machine. The physician identified 81% of the patients diagnosed psychoneurotic (74% in men and 86% in women), while the machine identified only 42% (45% in men and 39% in women).

Data in Tables 3 and 4 reveal that in some cases the physician was able to identify the patient's diseases from the CMI when the machine method was unable to do so. In these cases the machine must be considered in error, since there were sufficient data on the CMI to permit the making of the diagnoses. In other cases, neither the physician nor the machine could make the correct diagnoses from CMI data. Here either the CMI did not collect pertinent information or the patient was asymptomatic.

Table 3 shows further that in 15% of cases (14% in men and 15% in women) the machine correctly identified disorders from data on the CMI when the physician did not do so. In these cases, the superior-

TABLE 5.—*Incidence of Correct and Incorrect Diagnoses by Machine Method and by Physician Interpreting CMIs of 350 General Medical Patients*

	Diagnoses/Patient, No.	
Evidence in Hospital Records	By Machine	By Physician
Diagnosis correct	2.3	2.9
Differential diagnosis correct	2.8	1.3
Diagnosis not correct	0.3	0.1
No information about diagnosis	0.7	0.8
Total	6.1	5.1

ity of the machine method can be ascribed to the fact that the machine is not influenced by fatigue or emotional factors in its access to an accurate memory, in the analysis of a large body of data, and in the making of its decisions.

Table 5 shows the incidence of false diagnoses made by the machine method and by the physician. Data for this Table were derived from the hospital records of the 350 general medical patients. For diagnoses not listed in the hospital summaries, the records were searched for evidence to confirm or disprove each of the diagnoses made by the machine or by the physician. Such evidence for the presence or absence of disease was found in the recorded histories, physical examinations, and laboratory examinations.

It is obvious from Table 5 that the machine made few false diagnoses. Of the average of 6.1 diseases per patient diagnosed by the machine method, the hospital records contain evidence that only 0.3 diagnoses per patient (4.9%) were incorrect. The physician diagnosed an average of 5.1 diseases per patient; the hospital records contain evidence that 0.1 diagnoses per patient (2.0%) were incorrect. Statistically, there is no significant difference between the incidence of incorrect diagnoses made by the machine and by the physician. The fact that the machine diagnoses are valid so frequently, as often as are those made with the same data by a physician, indicates that diagnoses made by the machine method deserve further investigation.

Comment

It was required of the machine system that it develop empirically its own diagnostic criteria. No a priori information, based on the experience and knowledge of the medical profession, was made available to it. Instead, the machine system was instructed how to determine diagnostic syndromes, from each patient's sex, age, and medical complaints, correlated with hospital diagnoses. These were the only data of which the system had knowledge. Beyond set programs, the machine was given no human assistance in its development and use of the syndromes.

By following instructions, the system identified syndromes of complaints on the CMI characteristic of the diseases studied here. The syndromes "discovered" independently by the machine proved to be in all important aspects those already known to the medical profession.[4] With use of diagnostic criteria it had developed itself, the machine evaluated correctly patients' symptoms in as many instances as did a physician, who used the same information and referred to criteria established by the accumulated experience of the medical profession. The superiority of the physician in diagnosing psychoneurosis appears to be a consequence of his having knowledge of a large number of cases of this protean disorder, both from his own experience and from the reports of others. The machine did not have the benefit of this knowledge.

A statistical method of making diagnoses can be used with medical data of many kinds. Because they were immediately available, the data used in this methodological investigation were symptoms elicited with the CMI. The method, therefore, was subjected to a rigorous test, since the only data given to the machine were of a historical nature. If, in addition, the machine had been given diagnostically definitive data from physical and laboratory examinations, we would expect it to have been even more accurate in its diagnostic decisions.

The machine method is applicable not merely to the 60 diseases studied here; it may be extended to include any disease for which a sufficient body of diagnostically significant data can be obtained.

A multiple-screening technique, employing a suitable questionnaire and a machine system, may be a useful adjunct to physicians. It yields diagnoses that are generally as correct as those made from the same data by a physician, and the self-elicited history needed for the technique is easy to obtain. Since the method is accurate, consistent, rapid, and tireless, it may be of

assistance to the medical profession when large numbers of diagnostic evaluations are to be made and when the large number of physicians needed to make the evaluations are not available. Such situations occur frequently, for example, in the making of comprehensive diagnoses on patients admitted to a general hospital, in the making of surveys, in industry, and in the military services.

Final diagnostic decisions cannot, of course, be made from data on the CMI about diseases that can be identified with certainty only by physical or laboratory examination. With these diseases, data from a history merely permit a recognition that the patient has a constellation of complaints that closely resembles complaints made by patients known to have the disease. In all cases, a diagnosis made by the machine from historical data is presumptive and can only suggest that the patient be examined for the likely presence of the disease.

In the study of patients of the 1956 sample, the machine did not in every case identify the diseases diagnosed in the hospital. Where it failed to do so, any of several causes may have been responsible. It may have been that the patient was asymptomatic or that the CMI or any medical history by itself provides insufficient data for the making of the diagnosis. For a given disease, a large number of undiagnosed cases in the 1948-1949 sample may have biased the diagnostic criteria identified by the machine system, or the population on which the machine system was tested may have differed from the one from which the diagnostic criteria were derived. Further, the machine method used may not be the most effective one it is possible to develop.

When the machine diagnoses a large number of diseases in a patient, the patient often has an emotional disturbance with complaints and "functional" disorders in many organ systems. Many of these patients had been diagnosed as psychoneurotic when they were examined in the hospital or, if they were included in the 350 cases whose CMI's were interpreted here by the physician, were suspected to be psychoneurotic by him.

The machine method designates not only the patient's disease but often those diagnoses that must be differentiated. It identifies in addition the likely presence of diseases unrelated to the patient's primary disorder.

In the comments here on the operation of the machine in making decisions there is no implied reference to the operation of thinking. The processes of making a decision may go on with or without thinking. For example, the machine system described here makes sophisticated decisions but, being a robot, does so without thinking. It can only follow instructions telling it how to analyze data in relation to past experiences so as to arrive at one or another predetermined conclusion. A thinking person, on the other hand, contemplating the same data and past experiences, can devise new methods of evaluating the data and can achieve previously unknown conclusions. A data-processing machine, following by rote the physician's instructions, is merely a mechanical extension of the physician's ability to remember, compare, compute, and decide.

Summary

A method is offered here by which presumptive diagnostic evaluations of a patient's complaints can be made, without the assistance of medical personnel, by a data-processing machine. The patient's complaints are self-elicited with the Cornell Medical Index-Health Questionnaire (CMI).

No information known to the medical profession was given the machine. Instead, the machine was required to determine for itself empirically the complaints characteristic of each of the 60 diseases most frequently diagnosed in a general hospital and to use this information in identifying the presence of any of these 60 diseases.

From data on the CMI alone, and at the rate of one second per patient, the machine correctly identified in 2,745 patients the presence of these 60 diseases 44% of the

times they had been found on hospital examination.

A physician and the machine independently interpreted the CMIs of 350 patients who underwent comprehensive medical investigation. The physician correctly identified 43% of diseases studied, other than psychoneurosis, when they had been diagnosed in the hospital, while the machine correctly identified 48%. The physician correctly identified 81% of instances of psychoneurosis, while the machine identified 42%. Of all the diagnoses made by the physician, 2% were false, as were less than 5% of those made by the machine.

The method described here may be of assistance to the medical profession in providing comprehensive medical appraisals of large numbers of people.

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Reduction of Serum Cholesterol Levels and Beta-Lipoprotein Cholesterol Levels by Nicotinic Acid

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Introduction

Because of the statistical relationship between hypercholesteremia and atherosclerosis, reduction in serum levels of cholesterol (especially the β-lipoprotein cholesterol fraction) has been the goal of numerous programs of treatment. In evaluating any form of therapy, three main questions must be answered: 1. Will it effectively reduce cholesterol levels? 2. Is it nontoxic and otherwise suitable for long-term use? 3. Does it prevent or retard the development of atherosclerosis?

Several groups of investigators have found nicotinic acid in large doses to be effective in reducing serum cholesterol levels in hypercholesteremic and normal persons.[1-13] Nicotinamide in equal dosage failed to produce or maintain reduction in cholesterol levels,[1,3] its action resembling that of a placebo.[7,11] Neither the mechanism of action of nicotinic acid nor the reason for the failure of the amide is yet understood.

No group has reported any toxic effects which would make nicotinic acid unsuitable for prolonged clinical use. The high therapeutic ratio of the drug in animals is well known.[14] A report of the occurrence of extensive fatty metamorphosis in livers of rats fed diets containing 1% nicotinamide [15] has led us to evaluate hepatic structure and function in patients who have taken the drug for long periods.

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This study was supported by grants from the National Heart Institute, American Heart Association, Wisconsin Heart Association, and Wampole Laboratories.

Studies in cholesterol-fed rabbits in two laboratories have shown that nicotinic acid not only reduced serum cholesterol levels but resulted in partial (and often striking) protection against atherosclerotic lesions of the aorta.[16,17] Conclusions drawn from these studies cannot, of course, be transferred to humans. Like all methods of therapy of hypercholesteremia, the use of large doses of nicotinic acid must be evaluated by controlled studies over a period of many years before its effect on human atherosclerosis and its complications will be known. Such studies are in progress in our clinic and elsewhere, but insufficient time has elapsed to assess the results.

To date we have studied about 70 patients, of whom about 50 are in the study at the present time. Fifteen have discontinued the study for various reasons, most of them unrelated to the effects of therapy. Excluding those still in the first 24 weeks of therapy, we can now present our experience with 44 patients studied for periods up to two years. Only the data from the first 56 weeks of treatment will be considered in this report.

Materials and Methods

Patients.—Patients in Group 1 (those starting in the first year of the study) were selected if the average of pretreatment serum cholesterol determinations exceeded 270 mg. %. An electrophoretic apparatus became available for use at the end of the first year. In Group 2 (those starting in the second year of the study) several patients were included with normal total cholesterol levels but elevated β-lipoprotein cholesterol fractions (BLC) or β/α_1 lipoprotein cholesterol ratios (referred to hereafter as the β/α_1 ratio).

The 44 patients included 30 men and 14 women. The average age of the men was 50, with a range of 33 to 64 years. The average age of the women

was also 50, with a range of 38 to 66 years. Clinical conditions present included previous myocardial infarction (17 patients), angina pectoris without electrocardiographic evidence of infarction (6), arteriosclerosis obliterans (3), previous cerebral infarction (3), diabetes mellitus (3), xanthelasmata (5), xanthoma tendinosum (1), premature arcus senilis (3), and no vascular diagnosis or physical evidence of hypercholesteremia (9). More than one of these conditions were observed in a number of the patients.

All patients in the study were treated on an ambulatory outpatient basis, except for occasional hospitalization as necessary for illness or operation. All patients were instructed to continue to eat as they had eaten before the study. Except for one man who had been following a low-fat diet and three patients on diets for diabetes, all patients were eating typical American diets. Occasional evaluation of reported daily intake of food indicated that such a generalization was justified. The caloric intake varied from 1,500 to 3,800 Cal. per day, with 35% to 60% of calories derived from fat.

Dosage Schedule.—Nicotinic acid was given initially in doses of 3 gm. daily, in divided doses after meals to minimize side-reactions. This dose was continued for 12 weeks in all patients. Then, if the serum cholesterol level was below 250 mg. per 100 cc., the same dose was continued. In a few patients, a maintenance dose of 1.5 gm. daily was tried, but, since this change was usually followed by a rise in serum cholesterol levels, we no longer use the smaller dose. If hypercholesteremia was still present at the end of 12 weeks, the daily dose was increased to 4.5 gm. If after six to eight weeks of this dosage the levels remained elevated, the dose was increased to 6 gm. daily and later to 7.5 gm. if necessary.

After 30 weeks of therapy with nicotinic acid, nicotinamide was substituted in equal dosage. After 12 weeks of this drug, nicotinic acid was resumed in the same dosage and further individualized if necessary. In a few patients whose cholesterol levels still did not return to normal, the dosage was increased to 9 gm. daily. The capsules used after the amide phase of the study contained, in addition to 375 mg. of nicotinic acid per capsule, 50 mg. of ascorbic acid, 2.5 mg. of riboflavin, 5 mg. of thiamine mononitrate, 1μg. of cobalamin concentrate, 0.5 mg. of pyridoxine hydrochloride, and 2.5 mg. of calcium pantothenate (Vastran Forte, Wampole).

Laboratory Tests.—Serum cholesterol levels were determined from 2 to 10 times before treatment in all patients. Patients in Group 1 reported every two weeks for the first year of treatment and every four weeks thereafter for fasting blood samples; patients in Group 2 reported every two weeks for eight weeks and every four weeks thereafter. In the first year of the study, only total cholesterol determinations were performed (Drekter method[18]). After the electrophoretic apparatus was obtained at the beginning of the second year, lipoprotein cholesterol fractions were determined (Boyd method, modified by McKenzie[19]), as well as total cholesterol (Zak, et al. method[20]).

After one year of study the following tests were done in 17 patients: complete blood cell counts, urinalyses, blood glucose, blood nonprotein nitrogen, sulfobromophthalein (Bromsulfalein), serum bilirubin, cephalin flocculation, thymol turbidity, alkaline phosphatase, transaminase (SGOT), total proteins, and electrophoresis of serum proteins. Needle biopsies of the liver were performed in 17 patients and the tissue examined independently by two pathologists.

Results and Comment

Table 1 shows the average changes in serum cholesterol levels for the entire series of patients. The values for each period of treatment represent averages of all determinations on all patients during that period. The results in Group 1 show that an average reduction of 52 mg. per 100 cc. (19%) occurred in the first 12 weeks of treatment. The value for the 12- to 30-week period was only slightly lower but would have been still lower (as a result of larger doses in more than one-half of the patients) except for the trial of a smaller dose (1.5 gm. daily) in two patients for 6 weeks, which raised the average. When nicotinamide was substituted, the average levels rose to approximately the same value as the pretreatment average. Further treatment with nicotinic acid resulted in reduction similar to the initial response. In Group 2 the lower pretreatment average and less striking re-

TABLE 1.—*Average Serum Cholesterol Levels* After Treatment with Nicotinic Acid and Nicotinamide*

Group	Pts. No.	Before Therapy	After Therapy 0-12 Wk. (N. A.)	12-30 Wk. (N. A.)	30-42 Wk. (Amide)	42-56 Wk. (N. A.)
1	26	325	263	259	331	277
2A	9	315	278	274	342	—
2B	9	301	262	248	—	—

* Mg. per 100 cc.

TABLE 2.—*Changes in Plasma Cholesterol Levels During Nicotinic Acid Therapy*

Group		Patients, No. 12 Wk.	30 Wk.
1	Normal *	9	11
(26 patients)	Reduced †	9	10
	Not reduced	8	5
2	Normal *	7	10
(18 patients)	Reduced †	1	4
	Not reduced	10	4

* 250 mg. % or less.
† Lower by at least 40 mg. % but not normal.

sponse (average reduction of 38 mg. per 100 cc., or 12%) is explained by inclusion of several patients with normal or slightly elevated levels before treatment.

Table 2 shows the status of serum cholesterol levels at the end of 12 weeks and after 30 weeks. Responses are classified as normal (less than 250 mg. per 100 cc.), significantly reduced (by more than 40 mg. per 100 cc.), or not reduced. These designations are admittedly arbitrary but are convenient for expressing the results briefly. In both groups the effect of increased doses is shown by the improvement in responses in the 12- to 30-week period.

Table 3 examines the results in Group 2 further, showing changes in average values for the β- and α_1-lipoprotein cholesterol fractions. The normal values for these determinations are not clearly defined. Data from the Mayo Clinic show that 95% of normal women between the ages of 20 and 40 have β/α_1 ratios less than 3.8[11]; our data are similar, with 95% of the same group less than 4.2.[23] For the β-lipoprotein cholesterol (BLC) fraction we are tentatively considering 200 mg. per 100 cc. as the upper limit of normal, although it is probable that a lower value may eventually prove more suitable. Since the patients in Group 2 were selected because of elevated β/α_1 ratios and not because of the BLC values, 10 of the 18 had BLC levels of less than 200 mg. per 100 cc. before treatment. If we found these values today on routine screening tests (BLC less than 200), we might not suggest treatment. However, these patients were studied initially because of clinical evidence of vascular disease, and the 10 patients with BLC less than 200 mg. per 100 cc. include 6 cases of coronary artery disease in young men. Since we are unable to say whether the total cholesterol, β/α_1 ratio, or BLC represents the best predictive test for atherosclerosis, we are continuing to use all three values. In spite of the conclusions of the committee, which last year reported that ultracentrifuge data add nothing in predictive value to blood cholesterol determinations,[22] our data from electrophoresis of lipoprotein cholesterol fractions, like those of other workers, suggest that the β/α_1 ratio and the BLC level may be more closely correlated with clinical evidence of atherosclerosis than the serum cholesterol level.[23] Table 3 shows that the averages of β/α_1 ratios and BLC fractions were reduced to normal during therapy with nicotinic acid but rose to pretreatment values when nicotinamide was substituted. The α_1 fraction was increased slightly but not as much as the β fraction was reduced. There is no doubt that this represents a shift in cholesterol from one lipoprotein fraction to another. α_1 levels higher than 100 mg. per 100 cc. have been observed during administration of nicotinic acid, whereas levels above 60 mg. per 100 cc. have not been encountered in untreated patients.

Table 4 shows that the β/α_1 ratio was reduced to normal in most patients of Group

TABLE 3.—*Average β- and α-Lipoprotein Cholesterol Levels* After Treatment with Nicotinic Acid and Nicotinamide (Group 2)*

Group		Before Therapy	After Therapy 0-12 Wk. (N. A.)	12-30 Wk. (N. A.)	30-42 Wk. (Amide)
2A	β	204	159	155	228
(9 pts.)	α_1	45	57	62	54
	β/α_1	5.0	2.9	2.8	4.6
2B	β	196	152	151	—
(9 pts.)	α_1	39	56	58	—
	β/α_1	7.0	3.1	3.1	—

* Mg. per 100 cc.

TABLE 4.—*Changes in Lipoprotein Cholesterol Fractions in Group 2—Eighteen Patients*

		Patients, No.	
		End of 12 Wk.	End of 32 Wk.
β/α_1 Ratio	Normal *	14	15
	Reduced	2	1
	Not reduced	2	2
β-Fraction (10 normal before therapy)	Normal †	13	17
	Reduced	4	0
	Not reduced	1	1

* 3.5, or less.
† 200 mg. %, or less.

2 by 3 gm. of nicotinic acid daily (0-12 weeks) and that the results were improved still further by increased doses (12-30 weeks). The same remarks apply to the BLC fraction. It should again be noted that 10 patients had values for this latter determination of less than 200 mg. per 100 cc. before treatment. Comparison of this table with Table 2 shows that the β/α_1 ratio and BLC were frequently normal after treatment when the total serum cholesterol level remained above normal.

Table 5 shows lipoprotein values in patients of Group 1 after 30 weeks of nicotinic acid, after 12 weeks of nicotinamide, and 2 weeks after resumption of nicotinic acid. Values were obtained at these points on as many patients of Group 1 as possible, although equipment had not been available for pretreatment determinations in this group. The striking difference between the action of nicotinic acid and nicotinamide is again shown. It is also noted that after nicotinic acid therapy the average BLC levels were within the normal range while average

TABLE 5.—*Reduction of Serum Cholesterol Levels * After Nicotinic Acid and Nicotinamide*

Group		N. A. (30 Wk.)	Amide (12 Wk.)	N. A. (2 Wk.)
1A	Cholesterol	284	374	311
(10 pts.)	BLC †	161	234	181
1B	Cholesterol	—	357	287
(7 pts.)	BLC †	—	240	156

* Mg. per 100 cc.
† β-lipoprotein cholesterol.

total cholesterol levels were somewhat above normal. The BLC fraction was above 200 mg. per 100 cc. in 12 of these 15 patients after nicotinamide therapy; two weeks later, after resumption of nicotinic acid, only 2 of the 15 had BLC levels above 200 mg. per 100 cc., showing the prompt reduction in this fraction.

As in the Mayo Clinic series, our female patients showed greater reduction in serum cholesterol levels than the males, when the response to 3 gm. per day is considered. Table 6 shows that in the 11 women in

TABLE 6.—*Reduction of Serum Cholesterol Levels * by Nicotinic Acid—Comparison of Response in Men and Women in Group 1—Twenty-Six Patients*

	Pts., No.	Before Treatment	After Treatment	
			0-12 Wk.	12-30 Wk.
Women	11	330	257 (−22%)	260 (−21%)
Men	15	320	267 (−17%)	277 (−20%)

* Mg. per 100 cc.

Group 1, the 0-12 week average was 257 mg. per 100 cc., 22% lower than the pretreatment average of 330 mg. per 100 cc. The 15 men in this group showed an average of 267 mg. per 100 cc. for the 0-12 week period, 17% lower than the pretreatment average of 320 mg. per 100 cc. However, the 12- to 30-week averages, showing the effect of increased doses in 12 of the men and 8 of the women (as well as reduced doses in 2 of the women) were 260 mg. per 100 cc. for women (21% reduction) and 257 mg. per 100 cc. for men (20% reduction). These data suggest that the hypocholesteremic response to 3 gm. of nicotinic acid daily is greater in women but that results are equal in men and women when dosage is increased as outlined (Material and Methods). However, it is doubtful that such detailed conclusions are justified in such a small group with relatively slight differences in the averages. Only 3 of the 11 women were premenopausal; reduction of cholesterol levels was

TABLE 7.—*Reduction of Serum Cholesterol Levels * by Nicotinic Acid—Comparison of Response According to Pretreatment Levels*

	Pts., No.	Before Treatment	After Treatment	
			0-12 Wk.	12-30 Wk.
Below 320 mg. %	29 (9F, 20M)	286	252 (−12%)	249 (−13%)
320 mg. % or higher	15 (5F, 10M)	365	287 (−21%)	280 (−23%)

* Mg. per 100 cc.

not greater in these patients than in the others.

When average values are considered, persons with higher cholesterol levels showed a greater reduction than those with relatively slight hypercholesteremia. Unlike the Mayo Clinic group, we cannot attribute this observation to a larger number of women in the former group of patients. Table 7 shows that persons (29 patients, 9 women) with initial serum cholesterol levels less than 320 mg. per 100 cc. had an average level before treatment of 286 mg. per 100 cc.; the 0- to 12-week average was 252 mg. per 100 cc. (12% reduction), and the 12- to 30-week average was 249 mg. per 100 cc. (13% reduction). The persons (15 patients, 5 women) with pretreatment serum cholesterol levels of 320 mg. per 100 cc. or more had a pretreatment average of 365 mg. per 100 cc.; the 0- to 12-week average was 287 mg. per 100 cc. (21% reduction), and the 12- to 30-week average was 280 mg. per 100 cc. (23% reduction).

Individual responses to various doses of nicotinic acid have been illustrated by graphs in a previous publication.[3] In addition to patients showing satisfactory reduction with 3 gm. daily, a number were seen who responded to 4.5 gm. and a number who responded to 6 gm. daily but not to smaller doses. When serum cholesterol levels less than 250 mg. per 100 cc. were the aim of treatment, doses higher than 3 gm. daily were required in more than 50% of patients. The response seems to be a highly individual matter, which is not predictable on the basis of age, sex, pretreatment average values, or clinical diagnosis. In the few refractory cases in which we have used daily doses of 7.5 gm. or 9 gm., results have not been better than those obtained with smaller doses. The few cases in which we tried 1.5 gm. as a maintenance dose early in the study responded with higher serum cholesterol levels, and it is no longer our practice to use doses smaller than 3 gm. daily, although there are probably some patients who could be maintained on smaller doses.

Side-Reactions.—Nearly all of the patients experienced a subjective and objective flush, with or without accompanying pruritus, for a short time after each dose of nicotinic acid for the first one to seven days of therapy. Table 8 shows the duration of these symptoms, as reported by the patients when we recently surveyed their side-reactions. We were surprised that 14 patients stated that they still had some flushing after every dose of nicotinic acid, inasmuch as few of them had mentioned the symptom on their visits for blood tests. When questioned, they stated that the flush was mild, not incapacitating, and not nearly as severe as it had been in the first week. In general, the flush decreased in intensity after the first day and usually subsided by the end of the first week. It did not interfere with therapy in any patient who persisted in taking the drug for one week or longer, with a single exception. After the first week or two, some patients flushed occasionally after the morning dose, after a small meal, after interrupted dosage, or when the drug was taken on an empty stomach. No flushing was caused by nicotinamide.

TABLE 8.—*Duration of Flushing in Patients Taking Large Doses of Nicotinic Acid*

Duration	Pts., No.	Average
Less than 10 days	24	4.8 days
10-30 days	8	15.5 days
Longer (every dose)	14	Every dose

Gastrointestinal irritation, consisting of nausea, vomiting, and occasionally diarrhea, was observed infrequently but led two pa-

Brown skin rash around periphery of axilla.

tients to discontinue therapy. Transient urticaria has occurred in a few patients but has not interfered with therapy. Thirteen patients have noted dryness of the skin. Two patients also had a brown rash in the axillae and at pressure points somewhat resembling acanthosis nigricans (Figure). The skin reaction subsided completely when nicotinamide was substituted and did not recur when nicotinic acid was again administered.

No significant changes in weight occurred, except for a loss of 20 lb. in one man who was moderately obese. His loss in weight was not accompanied by striking change in cholesterol levels from those in the periods before and after the period of weight loss. In our patients the reduction in serum cholesterol was not correlated with body weight, as in some of Altschul's patients, most of whom had normal cholesterol levels before treatment.[4,10] We did not measure the basal metabolic rate in our patients, as Altschul and Hoffer did,[4,10] but the absence of significant loss of weight in the group as a whole leads us to doubt the presence of a sustained increase of the basal metabolic rate.

Toxicity Studies.—No abnormalities were found in complete blood cell counts, urinalyses, blood glucose and nonprotein nitrogen, sulfobromophthalein retention, serum bilirubin, cephalin flocculation, thymol turbidity, transaminase, alkaline phosphatase, total proteins, and electrophoresis of serum proteins when these tests were performed in 17 patients after one year of the study.

Because of the study of Handler and Dubin, which demonstrated fatty changes in livers of rats fed large amounts of nicotinamide,[15] needle biopsies of the liver were performed in 17 patients after one year of study. No significant fatty metamorphosis or other morphologic abnormality was noted by two pathologists who independently examined the specimens.

In three diabetic patients, no evidence of significant effect on control of diabetes was observed. Neither glycosuria, hyperglycemia, nor appearance of overt diabetes in latent diabetics has occurred.

No deaths occurred in patients receiving nicotinic acid. Two patients had myocardial infarctions during therapy and recovered uneventfully, without interruption in dosage of nicotinic acid. In this respect our experience parallels that of the Mayo Clinic group. Patients with angina pectoris did not experience any increase in frequency or severity of pain; in fact, several of the patients reported that they had less angina than before treatment. However, great caution must be used in accepting statements of improvement in subjective symptoms in patients receiving a new form of therapy under the supervision of interested and sympathetic physicians; for this reason we do not wish to overemphasize the reported diminution in anginal symptoms.

Comment

Nicotinic acid in large doses represents an effective and apparently safe method of reducing serum cholesterol levels in the

majority of hypercholesteremic patients. All studies reported to date are in agreement on these points. Our data show that the β-lipoprotein cholesterol fraction and the β/α_1 ratio are frequently reduced to normal while the total serum cholesterol remains somewhat above normal. The α_1 fraction is increased somewhat, but the major change is the reduction in the β fraction.

We have not found any means of predicting the response in serum cholesterol levels in any individual case, except possibly that patients with xanthoma tuberosum or xanthoma tendinosum are usually relatively refactory. Although the average reduction, both in milligrams per 100 cc. and in per cent of starting level, was better in those with higher pretreatment levels, this information does not permit accurate prognostication in the individual case. The response to therapy is a highly individual matter and can be ascertained only by trial and observation.

The fact that nicotinamide is ineffective in reducing serum cholesterol levels or in maintaining the reduction following use of nicotinic acid may be a clue to the mechanism of action of the latter. If the mechanism of action were known, it would probably be possible to find other related compounds which might be even more effective. Our studies related to this aspect of the problem have not progressed to the point where significant results can be reported. Urinary excretion products of nicotinic acid and nicotinamide are being measured to determine first whether there are significant differences. The possibility is also being explored that an intermediary metabolite is formed from nicotinic acid but not from nicotinamide in sufficient quantities to be active in affecting cholesterol metabolism. The fate of C^{14}-cholesterol during control periods and treatment periods will also be studied. Studies bearing on this general subject are being done by others, and we await the results eagerly.

The effect of nicotinic acid therapy on atherosclerosis remains to be seen. The experiments on rabbits are impressive.[16,17] In humans, we are expanding our series to insure long-term follow-up on a sufficient number of patients to produce significant results when compared with controls over the next 5 to 10 years. We have recently observed a case in which xanthoma tuberosum decreased strikingly in four months of therapy with 3 gm. of nicotinic acid daily. Achor, Berge, and associates have observed complete disappearance of xanthelasmata of the eyelids in one patient treated for two years; decrease in size of xanthelasmata and of xanthoma tendinosum has occurred in other patients under their observation.[23]

Summary and Conclusions

1. Serum cholesterol levels can be reduced in the majority of hypercholesteremic patients by administration of large doses of nicotinic acid while the patients continue to eat their usual diets. The reduction is most prominent in the β-lipoprotein cholesterol fraction, with reduction of the β/α_1 lipoprotein cholesterol ratio.

2. Nicotinamide is ineffective in reducing serum cholesterol levels.

3. The only significant side-effects after ingestion of nicotinic acid are flushing and pruritus, which subside rapidly in the early stages of therapy and have not interfered with therapy. No toxic reactions have been found by clinical and laboratory observations, including a battery of seven tests of hepatic function and needle biopsies of the liver in 17 patients after one year of therapy.

4. Study for a much longer period will be required to determine whether this form of therapy for hypercholesteremia will prevent or retard the progression of atherosclerosis in humans as it does in cholesterol-fed rabbits.

Nicotinic acid was supplied by Eli Lilly and Company, Indianapolis, and Walker Laboratories, Inc., Mount Vernon, N. Y. Nicotinamide was furnished by Eli Lilly and Company and Nicotinamide and Vastran Forte was furnished by Wampole Laboratories, Stamford, Conn.

Laboratory determinations were performed by Mrs. Mary Bennett and Mrs. Phyllis Van Buskirk.

Liver biopsies were performed by Dr. John R. Steeper and Dr. Luther E. Holmgren, both of the Jackson Clinic. The biopsy specimens were reviewed by Dr. Etheldred L. Schafer, of the Jackson Clinic, and by Dr. Walter H. Jaeschke, of the University of Wisconsin Medical School.

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Case Reports

Interventricular Septal Defect Secondary to Nonpenetrating Injury

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Introduction

Interventricular septal defects resulting from nonpenetrating trauma are rarely diagnosed antemortem. In 1952, Pollock et al.[7] reviewed the literature and found 12 cases to which they added 1 autopsied case of isolated rupture of the healthy interventricular septum. Recently, Cary and Hurst[2] reported one additional case diagnosed at autopsy. The first recorded case established by cardiac catheterization was reported by Guilfoil[3] in 1953. We have not found any other catheter-proven cases resulting from nonpenetrating injury. Two surviving cases are presented.

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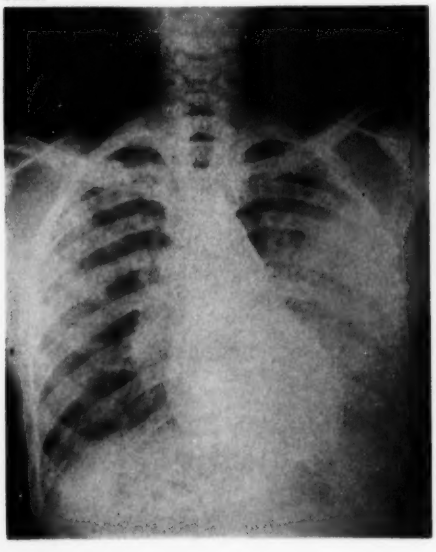
From the Radiology Service, 2349th USAF Hospital, Parks Air Force Base, Calif.

Fig. 1A.—Erect chest film, 24 hours after injury, showing pulmonary contusion and increased vascularity. The heart is not enlarged. Reproduced with permission from Histopathology Center, 2349th USAF Hospital, Parks Air Force Base, Calif.



Report of Cases

Case 1.—A 13-year-old boy was injured by a truck wheel passing over his thorax on Aug. 16, 1954. When he was hospitalized, a loud systolic murmur was audible over the entire precordium. Chest x-ray demonstrated pulmonary contusion, with normal cardiac size and configuration (Fig. 1A).

Prior to this accident, the child was active and in good health.

Apparent recovery occurred in two days, and the patient was discharged. However, owing to onset of progressive dyspnea and edema, the patient was referred to the University of Arkansas Medical Center on Sept. 11, 1954.

Pertinent findings on admission to the Medical Center were a Grade 4 systolic murmur and precordial thrill, cardiomegaly, and cardiac decompensation. Chest fluoroscopy with erect and recumbent films (Fig. 1B) revealed generalized cardiomegaly and pulmonary hyperemia. Associated with these findings was failure to respond to therapy. Ventricular septal defect, probably traumatic, was considered the most likely diagnosis.

Right heart catheterization revealed elevated right ventricular pressure (62/0 mm. Hg) and oxygen saturation (14.2 vol. %), with a calculated left-to-right shunt flow of 8.7 liters per minute. Multiple ECG's revealed evidence of myocardial damage.

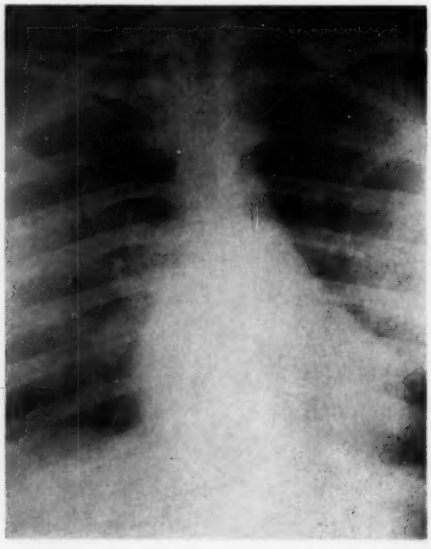
Surgical correction was undertaken elsewhere on March 23, 1955. Three ventricular septal defects were present near the apex; the largest (1.5×2 cm.) was surrounded by scar tissue extending to the ventricular wall. Complete closure of all defects was not accomplished.

The patient improved postoperatively and remained compensated after withdrawal of digitalis.

Fig. 1B.—Erect and recumbent chest films made four weeks after injury, demonstrating cardiac dilatation, pulmonary hyperemia, and no evidence of pericardial effusion. Reproduced with permission from Histopathology Center, 2349th USAF Hospital, Parks Air Force Base, Calif.

Fig. 1C.—Erect chest film, 1957, obtained two years postoperatively. Pulmonary vascularity is still slightly accentuated. Left ventricular enlargement, engorged pulmonary arteries, and a small aorta indicate a residual left-to-right shunt. Reproduced with permission from Histopathology Center, 2349th USAF Hospital, Parks Air Force Base, Calif.

Fig. 2A.—Recumbent (portable) chest film demonstrating cardiomegaly and increased pulmonary vasculature two days after injury. Reproduced with permission from Histopathology Center, 2349th USAF Hospital, Parks Air Force Base, Calif.



Follow-up in February, 1957, disclosed moderate limitation of exercise and easy fatigability. Chest x-ray (Fig. 1C) revealed cardiomegaly but no evidence of decompensation. Systolic murmur and an abnormal ECG persisted. The patient leads an essentially normal life.

CASE 2.—A 24-year-old airman incurred multiple injuries in an automobile accident on March 2, 1957. A severed femoral artery and comminuted femoral fracture on the left necessitated multiple transfusions and immediate surgery. Preanesthesia examination revealed a harsh Grade 4 systolic murmur, with thrill over the entire precordium.

Past history revealed multiple normal military and civilian physical examinations.

On the next day, after reoperation of the left thigh, the patient developed auricular fibrillation and cardiac decompensation. There was a good response to digitalis.

A recumbent chest film on March 6, 1957, revealed cardiomegaly to the left with pulmonary hyperemia (Fig. 2A). ECG was consistent with "posterior myocardial infarct."

In April, 1957, the patient was transferred to the USAF Hospital, Parks AFB, Calif. Upon arrival, fluoroscopy and film studies demonstrated combined ventricular enlargement and pulmonary hyperemia (Fig. 2B). Serial ECG's were consistent with healing and subsequently healed, "posterior septal infarct."

There was progressive improvement in the clinical and radiographic appearance. In June, 1957, the patient was judged stable and right heart catheterization verified the presence of a ventricular septal defect:

	Mm. Hg	O_2 Sat., %
Right ventricle (near tricuspid valve)	34/4	85
Right ventricle (mid-portion)	40/O	92
Pulmonary artery	29/7	87

Isotope dilution studies also indicated a left-to-right shunt.

The patient gradually resumed full ambulation. Digitalis was discontinued in June, 1957. By October, 1957, the patient's chest x-ray was normal except for slight prominence of pulmonary vascularity (Fig. 2C).

In January, 1958, the patient was symptom-free. Cardiac murmur and thrill were diminished in intensity but still present. Chest x-ray was unchanged in appearance (Fig. 2D). Cardiac catheterization was repeated in February, 1958. The findings are indicative of a decrease in the size of the defect:

	Mm. Hg	O_2 Sat., %
Right ventricle	34/O	84
Pulmonary artery	32/10	82

The patient is entirely stable. A healed but incompletely closed traumatic septal defect exists. No symptoms are present, and unless pulmonary

Fig. 2B.—Chest film, April 10, 1957, showing pulmonary hyperemia. Cardiomegaly is apparent only in retrospect. Reproduced with permission from Histopathology Center, 2349th USAF Hospital, Parks Air Force Base, Calif.

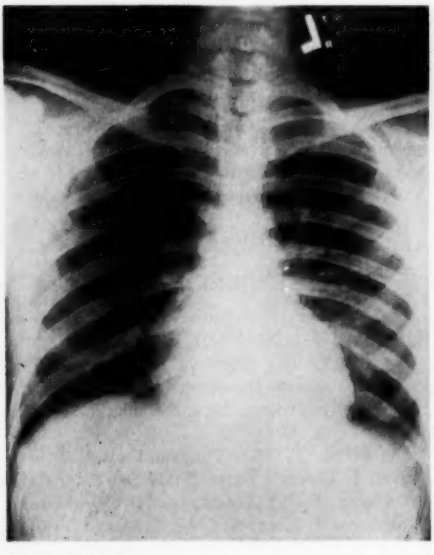


Fig. 2C.—Chest film, October, 1957, obtained immediately prior to cardiac catheterization. Cardiac size and configuration are normal. Pulmonary vessels are still accentuated. Reproduced with permission from Histopathology Center, 2349th USAF Hospital, Parks Air Force Base, Calif.

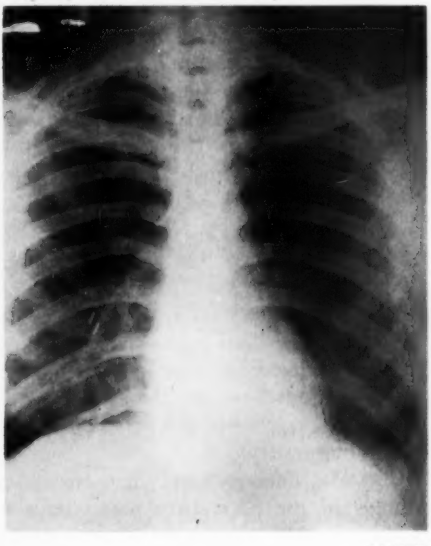


Fig. 2D.—Essentially normal chest film made in January, 1958, just prior to repeat catheterization. Reproduced with permission from Histopathology Center, 2349th USAF Hospital, Parks Air Force Base, Calif.

hypertension ensues no surgical corrective measures are planned.

Comment

Evidence of cardiac injury in cases of severe trauma is often unrecognized. Urbach [5] gave an incidence of 185 cases of cardiac injury in 1,000 autopsy cases with chest contusions. In 50 consecutive fatal automobile accidents, Leinoff [6] found macroscopic cardiac damage in 15% of the cases. In 1955, Halter [4] stressed the infrequence of antemortem diagnosis, and the need for early diagnosis of cardiac injury.

External evidence of chest trauma need not be present. Sudden compression of the legs and abdomen has produced septal rupture.[4] In our two cases and the case reported by Cary,[2] rib fractures were not demonstrated. Both cases recorded here had a prominent murmur and thrill when first examined; however, these findings are not always present early in cases of penetrating injury.

Clinical findings of nonpenetrating wounds of the heart have been discussed in detail in other articles.[1-3] Electrocardiographic findings are those of arrhythmia and evidence of myocardial damage, which both of our cases demonstrate.

Radiographic findings may be initially normal in relation to the heart as in Case 1. Evidence of cardiac decompensation and/or left-to-right shunt was ultimately present in both cases. Such findings in cases of severe trauma are indicative of cardiac injury and should cause one to consider ventricular septal rupture. The delay in onset of symptoms and of cardiomegaly in our first case further emphasizes Cary and Hurst's recommendation for delayed follow-up.[2]

Awareness of this lesion on the part of the radiologist may be of real service to the patient and his attending physician. Ventricular septal rupture should be included in the differential diagnosis of cardiomegaly secondary to any severe corporal trauma. Even in the face of an apparently normal heart radiographically, the recommendation for serial film studies may prevent subsequent catastrophe.

Summary

Early recognition of cardiac trauma is emphasized by presentation of two cases of traumatic interventricular septal defect arising from nonpenetrating injury. Lack of rib fracture and delay in onset of radiographic findings does not exclude severe cardiac injury.

Dr. David M. Gould, Chairman and Head, Department of Radiology, University of Arkansas Medical Center, permitted us to use Case 1, which was initially studied by us at that institution.

Dept. of Radiology, USAF Hospital, Lackland AFB, Texas.

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Staphylococcal Septicemia

Report of a Case with Hyponatremia and Eventual Recovery Through Use of Multiple Antibiotics and Adrenal Steroids

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Introduction

Staphylococcal septicemia represents a major problem in therapy despite the availability of numerous antibiotics. Mortality remains high,[1,2,5] and the course of the disease may be very prolonged.[1,3] The staphylococcus exhibits remarkable ease in developing resistance to antibiotics,[1-5] and for this reason it has become common practice to judge therapy with in vitro sensitivity studies, thereby leading to the use of multiple antibiotic agents concomitantly.

Report of Case

A 17-year-old white soldier entered the hospital April 6, 1957, with sudden onset of anterior chest pain; three days earlier he developed dysphagia and nonproductive cough followed by headache, chills, fever, and retrosternal discomfort. The past history and family history were irrelevant.

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From the Medical Service, U. S. Army Hospital, Fort Carson, Colo.

On admission the physical examination disclosed an asthenic youth, moderately ill but oriented, with temperature of 104 F, mild tachycardia, and tachypnea. The oropharynx was mildly injected; splinting of the right hemithorax, diminished breath sounds, minimal dullness over the right lower posterior chest, and coarse basal rales on either side were present; a chest radiogram disclosed a patchy infiltrate in the right middle and lower lobes. The white blood cell count was 12,600, with 75% neutrophils. Therapy consisted of an intravenous infusion of 1,000,000 units of penicillin augmented by 600,000 units every 12 hours plus 1 gm. of streptomycin daily. Sputum for culture was unobtainable, but a blood culture was done. The patient remained toxic, at times disoriented, and exhibited irrational behavior during the next 40 hours. A lumbar puncture was performed with normal cellular and chemical constituents. By the third hospital day the patient was totally disoriented, lethargic, and desperately ill; a few petechiae were noted on the hands and feet, and a solitary hemorrhagic pustule on the hypothenar eminence was observed for the first time. The heart was normal except for a sinus tachycardia; the liver and spleen were not palpable. The nail beds were slightly cyanotic with no evidence of clubbing.

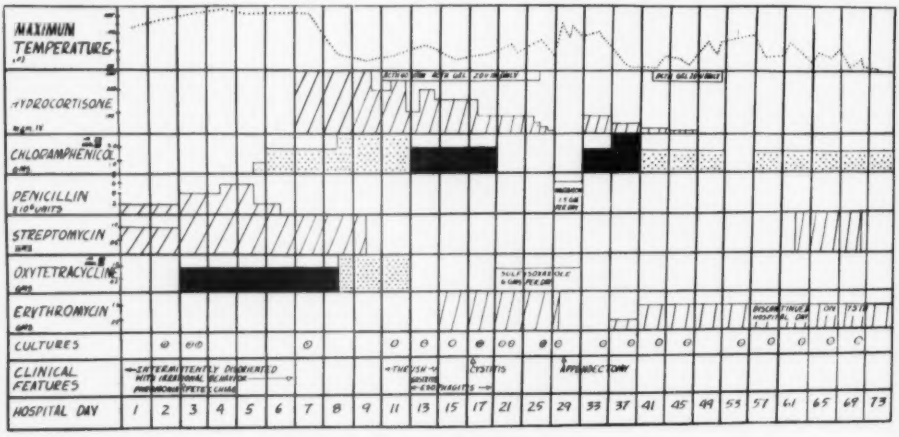

Figure 1

Because of the septicemia several additional blood cultures were obtained, and therapy was modified to include 4,000,000 units of aqueous penicillin by continuous intravenous infusion with 0.8 gm. of oxytetracycline, plus 1.5 gm. of streptomycin intramuscularly in divided doses daily for the next 72 hours. Little change in the patient's status occurred, except that more petechiae were evident. On the fifth day chloramphenicol, 500 mg. every six hours, was added to the infusion. By the sixth hospital day the patient deteriorated further, with the development of a hyponatremia unresponsive to massive salt replacement. Hydrocortisone therapy was instituted, 300 mg. during the first 24 hours; within 12 hours the patient's temperature had subsided to near normal, and he became alert and able to take food. On the seventh hospital day Staphylococcus aureus was identified in the *initial* blood culture, reportedly sensitive to chloramphenicol, slightly sensitive to oxytetracycline and streptomycin, and insensitive to chlortetracycline and penicillin (disk method). The patient was maintained on chloramphenicol, oxytetracycline, and streptomycin. Gradual improvement ensued thereafter in spite of several complications—oral moniliasis, esophagitis, and gastritis attributable to the antibiotics; hemorrhagic cystitis, and on the 30th hospital day an acute appendicitis requiring surgical intervention. Hydrocortisone was discontinued after two weeks, with a recurrence of fever, but reinstatement of steroid therapy was deemed unnecessary, particularly since the patient continued to show improvement. The blood cultures remained positive until the third week of treatment, following which they remained consistently negative (Fig. 1). A follow-up 10 months after onset of the disease found the patient clinically well.

Electrolyte studies done at frequent intervals are outlined in Figure 2. Of notable interest is the hyponatremic state (serum sodium, 110 mEq. per liter), appearing early and unaffected by the administration of large quantities of salt (exceeding 45 gm. of sodium chloride or greater than 750 mEq. of sodium per day) and in spite of a positive sodium balance in excess of 400 mEq. of sodium. Hydrocortisone arrested this dramatically, the serum sodium rising from 110 mEq. per liter to 128 mEq. per liter, and with a positive sodium balance of only 25 mEq.; concomitantly there was observed a decrease in the negative potassium balance.

During the course of the disease the continuing need for antimicrobial therapy was determined by culture and sensitivity studies. The sensitivity of the organism seemed to vary somewhat, becoming less sensitive to chloramphenicol and erythromycin and insensitive to all other antibiotics as time passed; these two agents remained as the most important antibiotics in effective control of the infection. Another interesting aspect was the lack of sensitivity of this organism to novobiocin, contraindicating its use from the very beginning and despite the fact that novobiocin had never been used in this hospital up to that time.

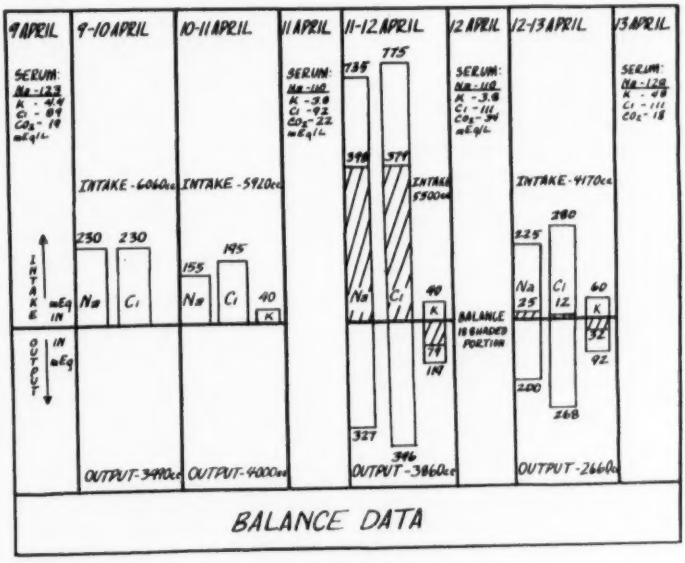

Figure 2

Comment

A case of staphylococcal septicemia secondary to a bronchopneumonia is presented. Points of particular interest are as follows:

(1) Eventual cure of an apparently overwhelming infection, with aid of steroids, by antibiotics usually considered bacteriostatic.

(2) Development of marked hyponatremia during the acute toxic phase, unresponsive to massive salt administration despite a markedly positive sodium balance (approximately 400 mEq.) but responding to steroid administration with a rise from 110 to 128 mEq. of sodium despite no significant positive sodium balance. This is postulated to represent the ability of steroids to restore cellular membrane integrity in maintaining selectivity between sodium and potassium; it has been previously suggested [6] that one cause of hyponatremia is "fatigue of the metabolic sodium pump," and previous communications [7,8] have reported correction of hyponatremia in edematous cardiacs with corticotropin (ACTH).

Summary

A case report of a 17-year-old youth with staphylococcal septicemia, presumably secondary to bronchopneumonia, is presented, with eventual recovery following use of multiple antibiotics and adrenal steroids. The hyponatremic state, unresponsive to massive salt replacement but dramatically corrected with hydrocortisone, is the interesting and outstanding feature.

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Multiple Peripheral Emboli in Atherosclerosis of the Aorta

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Multiple peripheral vascular occlusions are usually considered due to multiple emboli originating from thrombi in the chambers of the heart or from the heart valves. Less commonly large thrombi form on the walls of the aorta which may break off to occlude large peripheral vessels and produce massive infarcts. A rare condition which may produce multiple small emboli with a variegated clinical picture is embolism of atheromatous material subsequent to erosion of atheromas of the aorta.

Report of Case

The patient, whose final admission to the Mayo Clinic occurred on March 1, 1956, was a white man aged 69 years. His family history was noncontributory. In 1905 he was found to have syphilis. Apparently he had had adequate treatment for this, and there was no subsequent clinical problem related to this diagnosis.

In 1939, seventeen years before his final admission to the Clinic, he first experienced typical angina. Eleven years later, he had an acute myocardial infarction. Two years after this, a diagnosis of bilateral shoulder-hand syndrome related to coronary heart disease was made.

In 1943 the patient had his first episode of acute pain and redness in the region of his right great toe. A diagnosis of gout was made by his family physician. He was given a low-purine diet and tablets of colchicine to be taken when he had subsequent attacks.

Seven weeks before his final admission to the Clinic he awoke from a nap to find that he was blind except for light perception. His vision began to improve somewhat that day and continued to improve. The physician in his home community found thrombosis of the left central retinal vein. At that time his blood pressure was 200 mm. of mercury systolic and 100 mm. diastolic. His reflexes including his pupillary reflexes were equal and physiologic. Examination of the cerebrospinal fluid revealed no abnormalities. Anticoagulant therapy was begun and continued, and gradual improvement occurred.

At the time of his final admission he gave a history of mild intermittent claudication for seven months. About four weeks prior to this visit, some blotchy red marks had appeared on his legs and feet. Two days prior to this visit an episode of pain, redness, and swelling of the right wrist and of the left fourth toe had been relieved after taking colchicine tablets.

On general physical examination at the Clinic the heart was found slightly enlarged to the left, and there was a Grade 2, blowing systolic murmur, best heard at the apex. The pulse was regular, but there was a tachycardia with a rate of 120 beats per minute. Blood pressure was 190 mm. of mercury systolic and 110 mm. diastolic. The liver was enlarged and palpable 2 to 3 cm. below the right costal margin in the midclavicular line. He had a large right inguinal hernia. Scattered patchy, irregular purpuric areas were noted on the legs, feet, and thighs. The toes of both feet were purple on dependency; this was more marked on the left than on the right. Blanching of the toes occurred on elevation of the legs, with a slow return of color when they were again dependent. However, the peripheral pulsations in the dorsalis pedis and posterior tibial arteries were satisfactory.

The retinal arterioles were narrowed Grade 1 to 2, with retinal arteriolar sclerosis, Grade 2. Examination of the perimetric fields showed a scotomatous left homonymous hemianopsia, indicating some interruption of the central portion of the optic radiations in the right temporal lobe. To the ophthalmologist the patient's continued improvement suggested a vascular basis for the patient's condition.

Pertinent laboratory findings included the following ones: The urinalysis showed albuminuria, Grade 4, with occasional hyaline, granular, and leukocytic casts and with occasional erythrocytes. The value for hemoglobin was 9.6 gm. per 100 ml., with 3,230,000 erythrocytes and 5,900 leukocytes

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Section of Pathologic Anatomy (Dr. Sayre) and Section of Medicine (Dr. Campbell), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

per cubic milliliter of blood. The value for blood urea was 164 mg. and for serum uric acid 7 mg. per 100 ml. The Kline test was weakly positive; the Kahn test gave a 2+ reaction and the Hinton and Kolmer tests were reactive. The prothrombin time was 20 seconds. A roentgenogram of the chest showed evidence of infiltration in the right cardiophrenic angle, which was thought to be early pneumonitis. The heart appeared enlarged, with calcification of the arch of the aorta. A roentgenogram of the left foot showed arterial calcification. An electrocardiographic tracing revealed a cardiac rate of 98, with a sinus rhythm. The T-waves were inverted in standard Lead I and diphasic in Lead II. In the V-leads the R-waves were absent in Leads I and II and small in Lead III. The T-waves were inverted in leads V_5 and V_6. A blood culture was negative.

Six days after the patient's admission to the hospital, he had two episodes of nausea and vomiting associated with abdominal pain. Patchy discoloration of the skin of the abdomen developed. Blood pressure was 140 mm. systolic and 90 mm. diastolic. The pulse was 80 beats per minute and regular. The patient complained of pain, which seemed to involve his whole abdomen, but on examination there were no localizing findings. He had normal bowel sounds. At 7:10 p. m. that evening the patient complained of pain in his right leg and the dorsum of his right foot. He was somewhat confused. He died suddenly at 4 a. m. the next morning, March 7, 1956, one week after admission.

The clinical diagnosis was (1) coronary arteriosclerosis with an old myocardial infarction and angina pectoris, (2) essential hypertension with secondary impairment of renal function, (3) generalized arteriosclerosis with impairment of the circulation to the lower extremities, and (4) gout.

Necropsy Findings.—At necropsy the heart was enlarged, weighing 670 gm., but it maintained its usual contour. The coronary arteries were sectioned at intervals of approximately 3 mm., and a marked narrowing was found in the left anterior descending coronary artery, with the greatest narrowing about 2 cm. from its origin. At this point only a small lumen was seen. The left circumflex coronary artery was likewise narrowed and practically occluded at approximately 1 cm. from its origin. The right coronary artery was extensively narrowed approximately 1 cm. beyond its origin. Distally the artery was widely dilated and the lumen was completely occluded by red grumose material. Beyond this point the lumen was open. On further examination of the heart, by serial cross sections perpendicular to the axis of the ventricles, extensive scarring was found in the posterior portion of the heart, primarily in the subendocardial region of the myocardium. The scars were white and irregular and had led to thinning of the myocardium to approximately half the posterior thickness of the ventricular wall. Only slight portions of the scar extended into the apex. A similar but much less extensive white scar was present in the anterior wall. The valves of the heart were essentially normal.

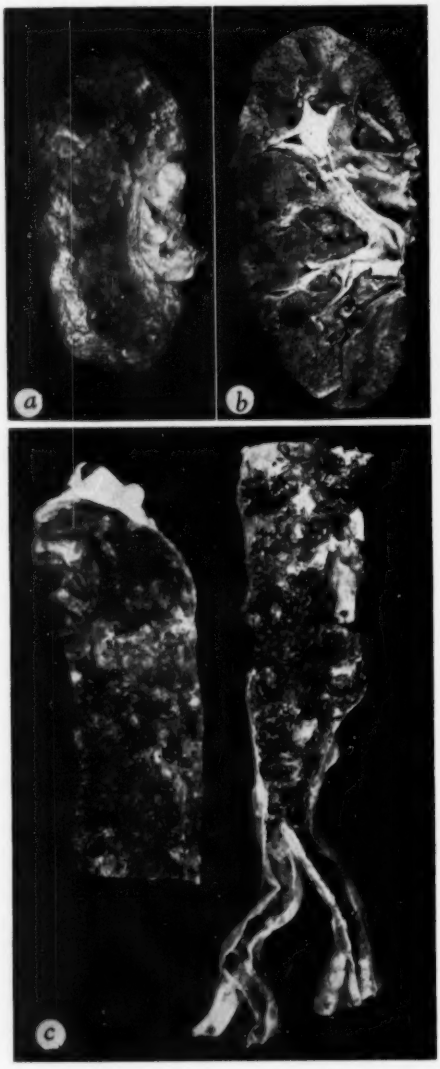

Fig. 1.—The kidneys and aorta. (*a*) The external surface of the kidney is irregularly rough and grossly granular. (*b*) Sectioned surface of the kidney demonstrates the narrowed cortex and the diffuse vascular thickening, without occlusion of the larger blood vessels. (*c*) Aorta with extensive atherosclerosis with erosions and blood and cholesterol precipitates.

Both lungs were heavy and firm and maintained their normal configuration. They were somewhat translucent and purple on external examination. When sectioned, considerable fluid exuded from the surfaces, approximately equally throughout. The right lung weighed 835 gm., and the left, 465 gm.

The spleen weighed 325 gm. and had maintained its normal external contour. The capsule was gray-blue. On section there was considerable mottling of the color from red to yellow. None of this, however, was well demarcated or focal in character.

The mucosa of the gastrointestinal tract was intact throughout. Distal to the ileocecal valve the colonic mucosa was dark brown to black in color, the quantity of color decreasing toward the sigmoid colon. No other internal or external lesions were visible. The liver, gallbladder, the pancreas, and the adrenal glands appeared essentially normal.

Both kidneys (Fig. 1*a*) were somewhat shrunken and were similar in appearance. The right kidney weighed 110 gm.; the left, 90 gm. The capsules stripped with moderate difficulty, revealing a rough granular surface with numerous depressions, some rather wedge-shaped and others flattened. When sectioned (Fig. 1*b*), the cortex was generally thinned, with variations in thickness. Some minor variations in color in a wedge-shaped distribution were seen, but these were not distinct. The pyramids, although essentially normal in appearance, had a few small oval areas of yellow discoloration toward the papillae, but the tips of the pyramids were not involved. The renal pelves, aside from being embedded in an excessive quantity of fat, appeared essentially normal. The walls of the blood vessels, when sectioned, were moderately thickened, and no occlusions or excessive atherosclerosis were visible.

When the aorta was examined, the external appearance was not particularly remarkable. The vessel was diffusely enlarged throughout its length and was relatively soft, without specific areas of dilatation or calcification. When the aorta was opened, however, the appearance was extraordinary. Instead of a relatively smooth intima with some atheromatous plaques, the intima was irregularly covered by masses of shaggy red fibrin-like deposits (Fig. 1*c*). This appearance began at the arch of the aorta, was particularly noticeable at the origin of the major vessels, and continued throughout the thoracic aorta, with a slight increase in the abdominal aorta. Only the root and ascending portions were unaffected. These changes extended slightly beyond the bifurcation into the left iliac artery, but otherwise the branches, though dilated, were not particularly involved. The shaggy areas were not associated with calcification or firmly formed fibrous plaques. Where the intima was still visible, it was slightly roughened, but linear streaking was not a prominent feature. Scraping away the shaggy deposits of fibrin revealed eroded atheromatous ulcers with loss of the inner lining of endothelium without a line of demarcation for the fibrin, atheroma, and underlying remaining intact aortic wall. The mouths of the major vessels could be identified, although partly obstructed by this deposit.

Finally, examination of the brain disclosed moderately severe atherosclerosis of the major vessels. This was most prominent in the basilar-vertebral artery system; the left vertebral artery contained an arteriosclerotic aneurysm, and the right vertebral artery was small and almost completely occluded. Focal loss of cortical substance was found at the right occipital pole and extended slightly along the mesial surface, essentially in the distribution of the right posterior cerebral artery. Investigation along this artery revealed focal occlusion some 3 cm. beyond its origin.

Histologic Findings.—The histologic findings could be divided into three groups: those related to coronary artery disease, those related to disease of the aorta and small arteries, and those related to gout.

The coronary arteries were partially occluded by the classic lesions of atherosclerosis. The right coronary artery had been occluded previously by a thrombus, which was now organized and partially canalized. In both major branches of the left coronary artery marked intimal proliferation with degeneration had narrowed the lumen to a fourth its original size.

Representative sections of the heart muscle revealed fibrous tissue replacement of focal areas of muscle in the posterior basal, lateral, and apical anterior parts. In addition there were focal areas of acute necrosis in the subendocardial muscle throughout the left ventricle. The innermost-lying muscle fibers and endocardium were intact and without evidence of thrombosis, and the small blood vessels, though they had thickened walls, were patent. On examination of representative sections of the lungs, the pulmonary alveoli were found to contain varying amounts of edema fluid. Many alveoli of the posterior portions of the lower lobes were partially collapsed. In the liver central congestion with central lobular necrosis of varying degree was evident, and the splenic pulp was congested.

Sections from the ascending aorta, the arch, the thoracic portion, and the abdominal aorta were stained with different methods for study.

In the ascending aorta the intima was intact and only slightly thickened. The elastic fibers of the media were not distorted, and the adventitial vessels and connective tissue were essentially normal. Beginning at the arch of the aorta marked changes could be seen in the intima, which was extensively

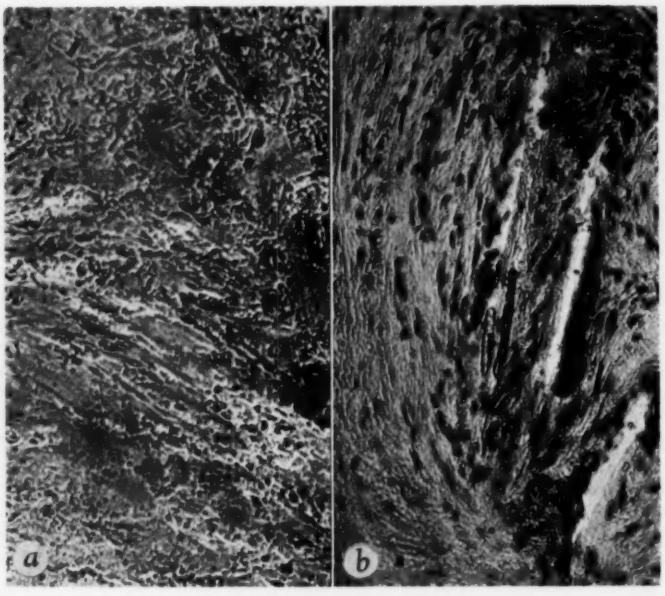

Fig. 2.—Acicular crystals in tissue cut on a freezing microtome and stained for fat. (*a*) Aortic atheroma with many acicular crystals. Sudan IV; reduced 10% from mag. × 200. (*b*) Interlobular renal artery showing acicular crystals in the biconvex clefts. Sudan IV; reduced 10% from mag. × 200.

thickened and distorted. This distortion was due partly to a simple increase in connective tissue. In many areas the connective tissue was replaced by a homogeneous granular material with large macrophages. Scattered in this material were many biconvex clefts and focal areas of erythrocytes. The endothelium did not cover these areas, and masses of precipitated erythrocytes extended from the lumen directly in continuity to the granular material. With stains for fat the granular material was seen to consist essentially of lipid in fine droplets, while acicular crystals were noted in many of the biconvex clefts (Fig. 2). The intima of the thoracic and abdominal aorta had a similar appearance. Fragmentation of the media was present in the thoracic portion. This was more pronounced in the abdominal portion and where it had led to a loss of half the thickness of the media. The adventitia was essentially normal throughout.

The small arteries of many of the remaining organs were occluded. These lesions were most conspicuous in the kidneys, where approximately one-fourth of the interlobular arteries were involved. All of the renal arteries exhibited diffuse intimal proliferation with distortion of the internal elastic tissue and medial atrophy of some degree. Such intimal changes were present in the occluded vessels as well. The occlusion was caused by masses of granulation tissue in which there were numerous biconvex clefts, occasionally associated with foreign-body giant cells (Fig. 3*a*). Longitudinally sectioned arteries occasionally were patent at one end and occluded by this material (Fig. 3*b*) at the other. In frozen sections acicular crystals, similar to those in the intima of the aorta, were seen in the clefts (Fig. 2*b*).

The remainder of the kidney cortex had the appearance seen in diffuse nephrosclerosis, with the greatest atrophy in the subcapsular region, and focal infiltration by mononuclear cells. No specific relationship could be demonstrated between atrophy and the vascular occlusions, and acute infarcts were conspicuously absent.

Similar vascular occlusions were noted in sections of the pancreas (Fig. 4*a*), spleen, liver (Fig. 4*b*), bone marrow, colon (Fig. 5*a*), one section of aorta, and the right posterior cerebral artery (Fig. 5*b*). In most organs the parenchyma was not damaged. In the pancreas, where an occasional vessel was occluded, mild interstitial fibrosis was associated. An occasional occluded vessel in the portal triads of the liver did not appear to influence the degree of central lobular necrosis. However, the occluded posterior cerebral artery was the cause of the old infarct at the right occipital pole of the brain.

At the time of necropsy, since the patient was known to have been suffering from gout, portions of the kidney had been fixed in alcohol to stain for uric acid. Focal masses of granular amorphous material were surrounded by degenerated and intact macrophages in the interstitial tissue of the medulla, corresponding to the yellow areas noted grossly (Fig. 6*a*). This granular material stained positively for uric acid (Fig. 6*b*), while the crystalline material in the blood vessels remained unstained.

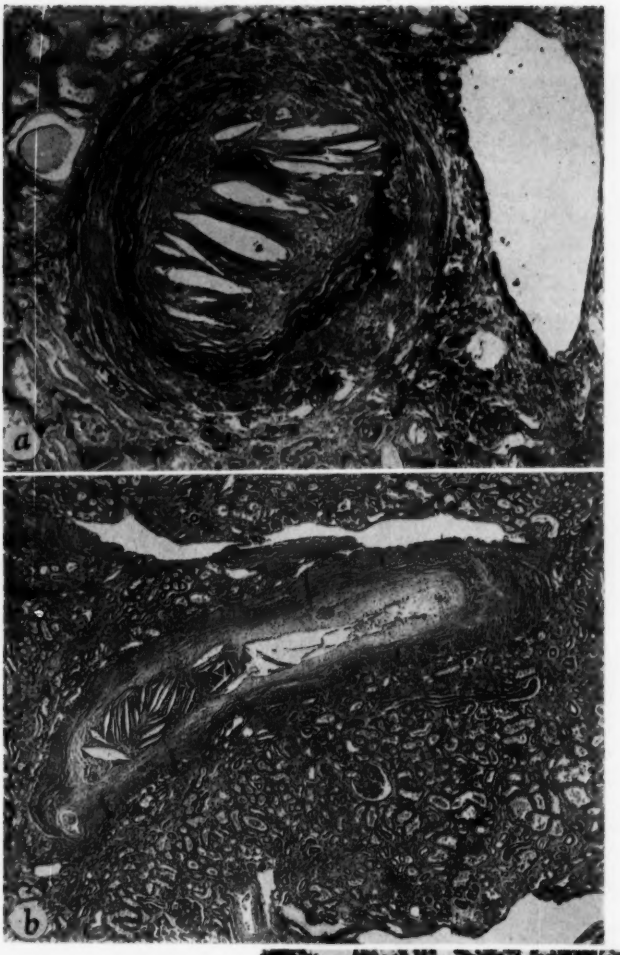

Fig. 3. — Interlobular renal artery. (*a*) Occlusion by granulation tissue containing many biconvex clefts, some surrounded by foreign-body giant cells. Mallory-Heidenhain stain; × 100. (*b*) Artery sectioned longitudinally. At one end the lumen is occluded by granulation tissue with many biconvex clefts; the other is free. Note the same degree of true endothelial hyperplasia at each end. Hematoxylin and eosin; × 30.

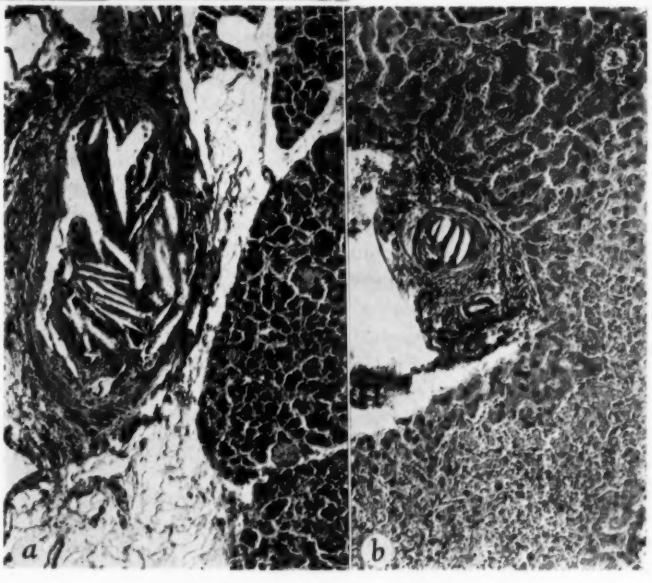

Fig. 4.—(*a*) Pancreas. Occlusion of a small artery. Hematoxylin and eosin; reduced 10% from mag. × 100. (*b*) Liver. Occlusion of a portal artery. There is also central lobular necrosis of liver cells. Hematoxylin and eosin; reduced 10% from mag. × 100.

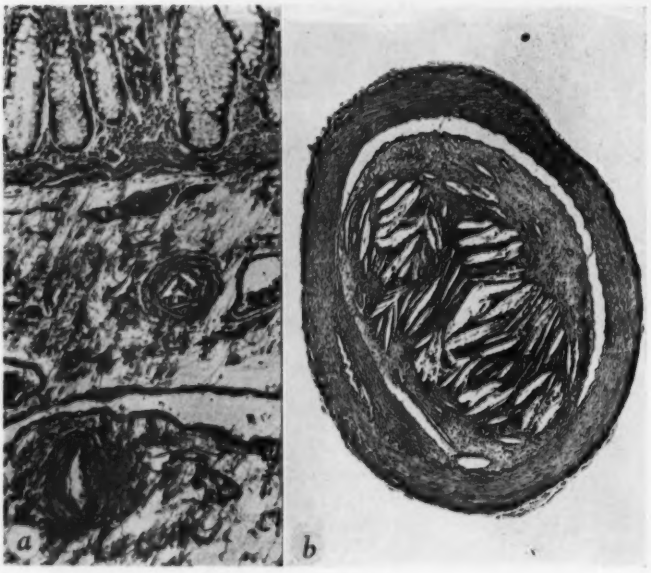

Fig. 5.—(*a*) Colon. A small submucosal artery is occluded without other demonstrable change. Hematoxylin and eosin; reduced 10% from mag. ×100. (*b*) Right posterior cerebral artery occluded by granulation tissue with biconvex clefts. Note minimal intimal fibrosis. Hematoxylin and eosin; reduced 10% from mag. ×40.

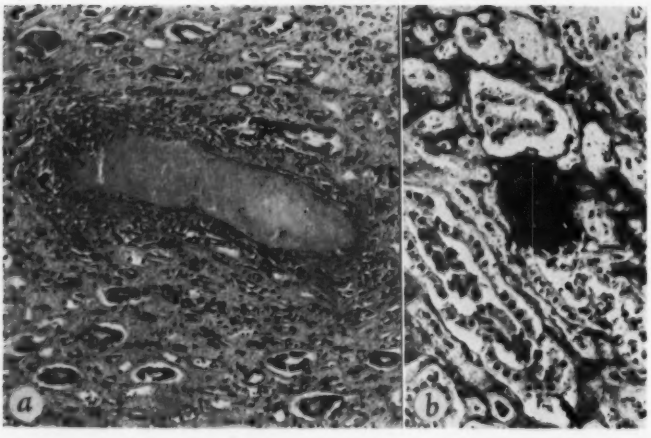

Fig. 6.—Renal medulla. (*a*) With hematoxylin and eosin stain a focal area of granular necrosis is evident next to tubules; reduced 10% from mag. ×100. (*b*) A neighboring section stained for urates, demonstrating that the granular material contains urates. Von Kossa's stain for urates; reduced 10% from mag. ×175.

Comment

Multiple emboli of atheromatous material in small arteries have been recognized only recently as significant lesions. Flory,[1] in 1945, gave the first definitive description of these lesions, and Meyer's[2] report, in 1947, apparently was made independently. Flory described in detail a case in which the aorta was markedly atherosclerotic with multiple erosions of the plaques. Histologically the plaques were filled with structureless gruel-like material containing cholesterol crystals. In some parts of the aorta the intima was eroded and mural thrombi containing crystalline spaces were superimposed. In 11% of the interlobular arteries of the kidneys the lumen was occluded by crystalline spaces partly surrounded by giant cells and hyperplastic connective tissue, with a few vascular channels. Some of the vascular lesions were associated with wedge-shaped areas of cortical atrophy. Similar vascular lesions were noted in the spleen, pancreas, and thyroid. Flory also reviewed 267 other cases of extensive atherosclerosis of the aorta. In

63 cases the atherosclerosis was severe in the aorta, but the plaques were not eroded, and no similar lesions were found in the small vessels. However, in 2 of the 147 cases in his series with slight-to-moderate erosion of the plaques and in 7 of 57 cases with advanced erosion occasional similarly occluded arteries were found. In two of these cases serologic tests had been positive for syphilis. Flory also injected atheromatous material removed from a human aorta into the veins of ears of two rabbits and later found similar lesions in the pulmonary arteries.

Meyer[2] reported similar arterial occlusion in two patients. In one the major occlusions were in the kidneys with associated deep scars; in the other many of the arachnoidal vessels were occluded, with associated focal areas of cerebral softening. Meyer suggested that occlusion with atheromatous material should be added to the usual causes of cerebral infarction.

In 1949, Zak and Elias[3] added two more cases. The first patient had carcinoma of the prostate with a severe anemia. He had had an episode of unconsciousness four months before death. At necropsy, in addition to widespread metastatic carcinoma there was severe aortic atherosclerosis, with erosion of many of the atheromas. Multiple acute infarcts of the spleen and old infarcts of the kidneys were noted. Histologically the lumina of the vessels supplying these areas were plugged by amorphous material containing acicular crystals. The Schultz test for cholesterol was positive when applied to frozen sections of the lesions. Similar vascular occlusions were noted in many other organs. In their second case death was caused by acute myocardial infarction. Many small arteries in the infarcted heart muscle were occluded. The origin for the occlusive material appeared to be an eroded atheroma in the right coronary artery.

That large peripheral arteries can be occluded by similar material was noted by Candiani.[4] In limbs amputated for gangrene he found the major arteries occluded by similar material, which he suggested came from the aorta.

The suggestion by Traut and associates[5] that those lesions are specific lesions in gout is interesting. Their patient, a man 50 years old with a history of poorly controlled gout for 12 years, died of a ruptured atherosclerotic aneurysm of the abdominal aorta. They found the lesions primarily in vessels in the submucosa of the colon and pancreas, which they believed to be due to deposition of urates in the walls of the vessels with subsequent foreign-body reaction. They unfortunately were unable to prove the crystals to be urates. Mayne[6] studied the renal lesions in gout and reviewed the kidneys of 27 patients who died and the surgically removed single kidneys of 8 other patients. In none of these patients was the primary disease gout. He found deposits of uric acid in the interstitial tissue in the renal pyramids in 20 of the 35 cases. No vascular lesions similar to those reported by Traut and co-workers[5] were found.

The case under discussion has combined many of the features previously reported. The immediate cause of death appeared to be pulmonary edema due to acute and chronic myocardial infarction, caused by severe coronary atherosclerosis. The aortic lesion was one of severe atherosclerosis, with erosions of many plaques with precipitation of blood which became mixed with cholesterol. The vascular occlusions by emboli of this material appeared widespread, being most marked in the kidneys, as noted by Flory and Meyer, and also in the brain, as described by Meyer and as possibly occurred in Zak and Elias' first case. The patient suffered from gout and the lesions of gout were identified in the kidney, as described by Mayne, but these appeared independent of the lesions in the blood vessels. An old history of syphilis was present in two of the cases reported by Flory and appeared incidental to the primary disease. Whether the vascular insufficiency in the extremities was due to similar occlusion of large vessels, as reported by Candiani, or whether both this finding and

those of multiple ecchymoses over the thighs and abdomen were due to occlusion of multiple small vessels in these regions unfortunately was not determined.

Conclusion

That multiple vascular occlusions of small arteries may occur from emboli from eroded atheromatous plaques in the aorta is again emphasized. Significant lesions appear to occur primarily in the kidneys, brain, heart, and extremities. The concomitant presence of a positive serologic test for syphilis or the presence of gout appears fortuitous.

Mayo Clinic.

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Rickets Secondary to Chronic Hyperchloremic Acidosis in Ureterosigmoidostomy

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Hyperchloremic acidosis as a complication of ureterosigmoidostomy has been recognized for many years.[1] The occurrence of additional electrolyte changes of serum calcium and phosphorus compatible with the presence of osteomalacia has also been noted.[2] However, to our knowledge the development of juvenile rickets secondary to hyperchloremic acidosis has not been reported previously. The presence of this syndrome in a juvenile patient who had undergone bilateral ureterosigmoidostomy represents an unusual case and is of particular interest because of the dramatic improvement which occurred clinically and radiologically after therapy.

Report of Case

A 14-year-old white boy was admitted to the Community Memorial Hospital because of weakness, anorexia, headache, and pain in the knees on walking. He had been born with exstrophy of the bladder, and his history revealed the following types of treatment of this anomaly and its postoperative complications. In 1946, at the age of 4 years, bilateral ureterocolostomy was performed. An intravenous pyelogram made prior to the operation disclosed nothing abnormal. A year later the bladder was removed and abdominal skin grafts were applied. Intravenous pyelograms made at this time indicated good function and slight dilation of both calyces. A year later, 1948, the value for nonprotein nitrogen was 32 mg. per 100 cc. of serum and the pyelographic pattern was essentially unchanged. In 1950, when the patient was 8 years old, renal colic developed and a stone was removed from the right ureter. At this time the value for nonprotein nitrogen was 76 mg. per 100 cc. of serum and for carbon dioxide, 11.9 mEq. per liter of plasma. After treatment the value for nonprotein nitrogen was 40 mg. per 100 cc. of serum and for carbon dioxide, 23.8 mEq. per liter of plasma. The intravenous pyelogram showed moderate dilation of both calyces. A nephrostomy tube was left in place, and external drainage was employed for approximately two and one-half years. In 1951, this patient was hospitalized with a diagnosis of pyelonephritis. Specific gravity of urine from the nephrostomy tube was 1.007, and the urine did not contain albumin, sugar, or acetone. Pyuria was graded +3. The content of nonprotein nitrogen was 28 mg. per 100 cc. of serum, and the value for carbon dioxide was 21.6 mEq. per liter of plasma. A phenolsulfonphthalein test demonstrated a 49% excretion of the dye from the right nephrostomy tube in two hours. In 1953, when the patient was 11 years old, the nephrostomy tube was removed. An intravenous pyelogram showed evidence of bilateral hydronephrosis. After removal of the nephrostomy tube symptoms of anorexia, weakness, headache, and vomiting appeared at intervals, and the presence of chronic acidosis was first noted. Treatment consisted of the sporadic parenteral administration fluids, with small doses of Scholl's * solution.

In 1954, this patient again was hospitalized with a diagnosis of pyelonephritis. The value for sodium was 131 mEq. per liter of serum; potassium, 3 mEq. per liter of serum; carbon dioxide, 14 mEq. per liter of plasma; blood urea nitrogen, 32 mg. per 100 cc. An intravenous pyelogram made at this time showed satisfactory function bilaterally at five minutes, with moderate bilateral hydronephrosis and retention of dye on both sides at two hours.

In June, 1955, this patient was hospitalized with a diagnosis of torsion and orchitis on the left. The value for sodium was 138 mEq. per liter of serum; for potassium, 1.8 mEq. per liter of serum; for chlorides, 115 mEq. per liter of plasma; for carbon dioxide, 8 mEq. per liter of plasma; for blood urea nitrogen, 34 mg. per 100 cc., and for creatinine, 1.2 mg. per 100 cc. of serum. In September, acute appendicitis developed, necessitating appendectomy. At this time the value for chlorides was 119 mEq. per liter of plasma. The content of nonprotein nitrogen was 51 mg. per 100 cc. of serum, and the value for carbon dioxide was 19.8 mEq. per liter of plasma. In October,

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* Scholl's solution contains 140 gm. of citric acid and 98 gm. of sodium citrate per 100 cc.

1955, the patient was admitted to the urology service of the Community Memorial Hospital. He complained at this time of nausea, weakness, headache, pain in the knees, and difficulty in walking. At this admission only limited studies were done. Of chief significance was the value of 110 mg. per 100 cc. of serum for nonprotein nitrogen. After the intravenous administration of fluids this value decreased to 44 mg. per 100 cc. of serum and the patient was discharged, symptomatically improved. After this hospitalization he noted increasing weakness and progressive difficulty in walking. Episodes of anorexia, headache, and vomiting became more frequent and were less responsive to the occasional parenteral administration of fluids. On Jan. 1, 1957, the patient was admitted to the medical service of the Community Memorial Hospital. He was a pale, red-headed, prepuberal boy who appeared to be younger than his 14 years. Blood pressure was 120 systolic and 70 diastolic in millimeters of mercury; pulse rate was 70, and temperature, 98.6 F. His height was 63 in. and weight, 92 lb. The skin was dry. The chest was clear. At the costochondral junctions bilaterally there were small, symmetric enlargements. The heart was normal. The liver, spleen, and kidneys were not palpable. The testicles were palpable midway in the inguinal canal. There was a surgical scar in the lower part of the midabdomen. The penis was small, and only a scanty amount of pubic hair was present. The scrotal sac was empty. The lower extremities showed evidence of wasting of muscles. The knee joints appeared enlarged, without swelling, and were painful to weight-bearing and flexion. His gait was waddling, and he could walk only with assistance. The reflexes appeared active. Results of a rectal examination were normal. The prostate gland was small. The erythrocyte count was 4,620,000 per cubic millimeter, and the value for hemoglobin was 84 gm. per 100 cc. of blood. The leukocyte count was 8,950 per cubic millimeter, 66% being segmented neutrophils, 33% being lymphocytes, and 1% being eosinophils. Results of serologic tests of the blood were negative. The sedimentation rate was 3 mm. in one hour (Westergren). The value for nonprotein nitrogen was 78 mg. per 100 cc. of serum. The content of calcium was 6.8 mg. and of phosphorus, 2.5 mg. per 100 cc. of serum. The alkaline phosphatase was 21.2 Bodansky units per 100 cc. of serum. The value for carbon dioxide was 12.5 mEq. per liter of plasma. The content of sodium was 147 mEq. per liter of serum and chlorides, 120 mEq. per liter of plasma. The concentration of potassium was 3.6 mEq. per liter of serum. Total proteins amounted to 5.2 gm. per 100 cc. of serum, with 4.1 gm. of albumin and 1.1 gm. of globulin. One specimen of urine from the cloaca, obtained on the fifth day after treatment, had a specific gravity of 1.010; the hydro-ion concentration was 7.5. Albuminuria was graded +1; there was no sugar. Six to eight leukocytes per field were seen with the high-power objective. Roentgenograms showed advanced rachitic changes at the ends of the long bones (Fig. 1). The density of the skeleton showed no change, and the peridontal membrane was intact. All changes occurred at the epiphysial zones of the long bones. An intravenous pyelogram disclosed bilateral hydronephrosis, with satisfactory concentration of opaque material. Comparison of this film with a similar one made in 1954 showed no appreciable change (Fig. 2). Biopsy of a section of tissue from the distal end of the left tibia revealed foci of resorption of bone and replacement of connective tissue with occasional giant cells. There was evidence of increased destruction, as well as active formation, of bone (Fig. 3). Treatment initially consisted of infusions of M/6 lactate solution, followed by daily oral doses of 100 cc. of Scholl's solution, 50,000 units of calciferol (vitamin D_2), 20 gm. of calcium gluconate, and 10 cc. of Potassium Triplex Solution.† This

† Potassium Triplex Solution (Lilly) contains 0.5 mg. each of potassium acetate, potassium bicarbonate, and potassium citrate per 5 cc.

Fig. 1.—Classical rachitic changes at the epiphyseal zones. Note the width of the epiphyseal zones and the flaring of the metaphyseal portion of the bone adjacent to the epiphysis.

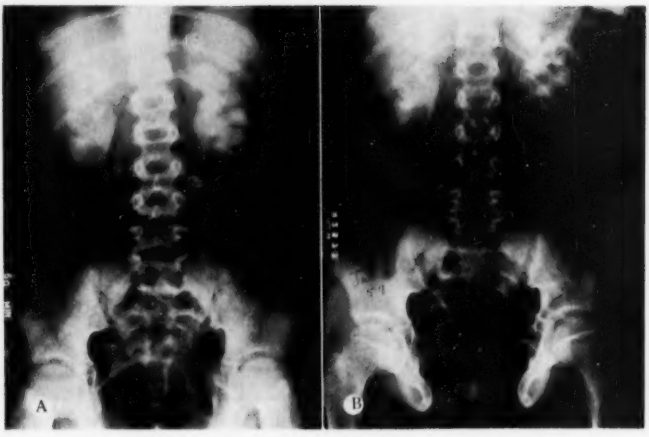


Fig. 2.—*A*, intravenous pyelogram made in 1954 shows satisfactory concentration and advanced hydronephritis. *B*, intravenous pyelogram made in January, 1957, shows the same relative degree of hydronephrosis and satisfactory concentration. Note the similarity between the two studies.

therapy brought about prompt subsidence of the nausea, vomiting, and headaches. The content of carbon dioxide gradually increased, and on the day of discharge, 10 days after therapy was instituted, it was 22.5 mEq. per liter of plasma. The patient was discharged with prescription of the foregoing oral medications. One month after the patient had been discharged the following values were recorded: calcium, 9.9 mg. per 100 cc. of serum; phosphorus, 5.1 mg. per 100 cc.

Fig. 3.—*A*, the normal marrow replaced by active mesenchymal tissue: myxo-fibro-fatty tissue. *B*, a palisaded row of "osteoblast-osteoclast" cells is adjacent to a pale-staining area of osteoid tissue. Normal bone is at the left of the photograph and is separated from osteoid tissue by a dark line. *C*, occasional foci of giant cells are seen here and there adjacent to areas of destruction and repair of bone. *D*, disorganized fragments of changed bony trabeculae lie embedded in fibrillar collagenous tissue.

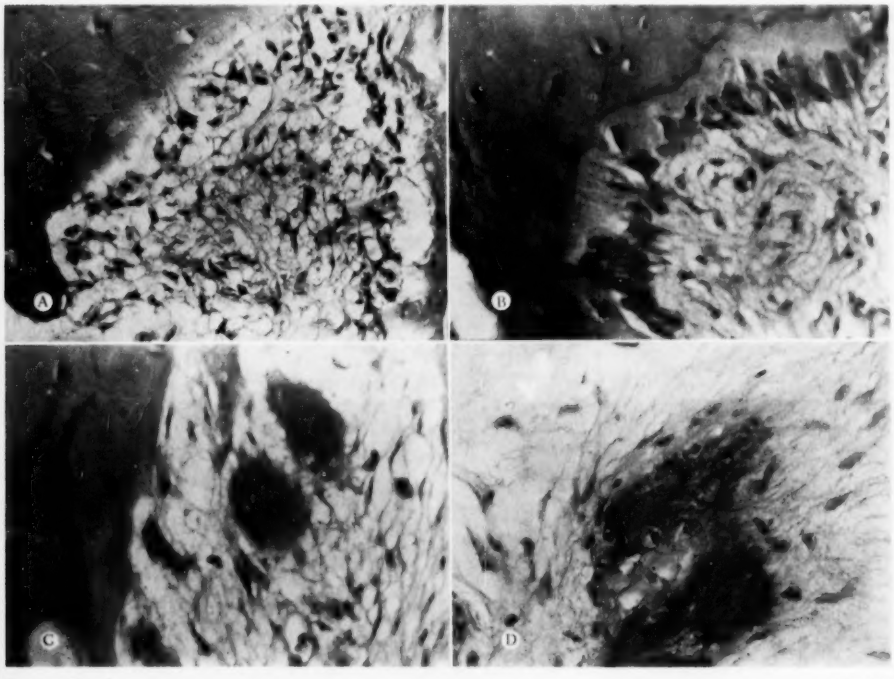


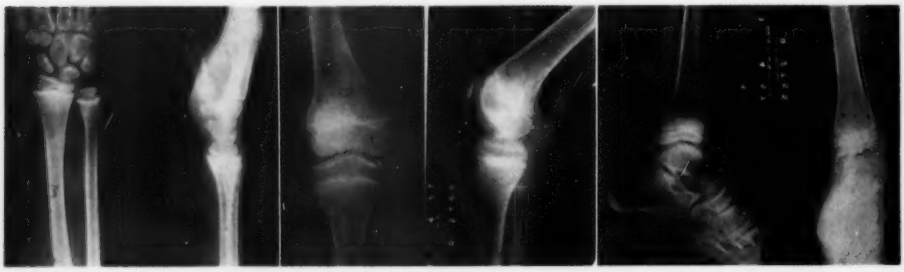
Fig. 4.—Note the marked ossification at the epiphyseal zones in a one-month period.

of serum; nonprotein nitrogen, 43 mg. per 100 cc. of serum, and alkaline phosphatase, 17.5 Bodansky units per 100 cc. of serum. The value for carbon dioxide was 19.3 mEq. per liter of plasma. The content of sodium was 140 mEq. per liter of serum and for chlorides, 131 mEq. per liter of plasma. Potassium was recorded as 4.8 mEq. per liter of serum. Roentgenograms of the ankles and wrists showed rapid ossification at the epiphysial zones (Fig. 4). Clinically, the patient was much improved. He could walk alone without pain, but his gait remained abnormal. All symptoms of nausea, vomiting, and headache had completely subsided. Two months after the patient had been discharged the value for calcium was 11.6 mg. per 100 cc. of serum and for phosphorus, 5.3 mg. per 100 cc. of serum. Nonprotein nitrogen amounted to 50 mg. per 100 cc. of serum; alkaline phosphatase, 9.4 Bodansky units per 100 cc. of serum. The value for sodium was 142 mEq. per liter of serum and for chlorides, 114 mEq. per liter of plasma. Potassium amounted to 5 mEq. per liter of serum, and carbon dioxide, 20.2 mEq. per liter of plasma. Roentgenograms of the wrist, knees, and ankles showed an advanced reparative process at the epiphysial zones (Fig. 5). Clinically, the patient was essentially normal. He had gained 10 lb. and felt well. For the first time in two years he was able to run. With the return to near normal of his blood components the use of all medications, except Scholl's solution, was discontinued. There had been no recurrence of symptoms to the time of this report.

Comment

The striking clinical and biochemical changes noted in this patient undoubtedly resulted from the prolonged divergence of urinary flow to the colon. The most significant of these changes were the presence of hyperchloremic acidosis, lowered values for serum potassium, calcium, and phosphorus, and the clinical and radiologic signs of rickets. Each of these changes and their mechanisms will be discussed separately, as will be treatment.

Fig. 5.—Note the advanced reparative process at the epiphyseal zones in a two-month interval.



Hyperchloremic Acidosis

Hyperchloremic acidosis frequently follows ureterosigmoidostomy. Ferris and Odel,[3] reporting on 141 patients with ureteral transplants to the colon, showed that 79% had some degree of hyperchloremia and 80% were acidotic at various times. Clinical studies by Parsons and associates[4,5] have shown that there is a marked absorption of sodium and chloride ions from the urine during contact of the urine with the colon. Further studies with radioisotopes by this group have shown that chloride ions are absorbed slightly in excess of sodium ions. However, in these cases the slight increase in absorption of chlorides over the absorption of sodium does not appear to be responsible for the state of hyperchloremia which results. Instead, the continued absorption of sodium and chloride ions in nearly equal amounts acts as an acid solution when presented to the extracellular fluids. This occurs because chloride ions are present in a lower concentration than sodium ions in the serum, and the continued addition of a solution containing equal numbers of sodium and chloride ions produces an excessive concentration of chlorides, with the subsequent development of hyperchloremic acidosis.

Reduction of Potassium, Calcium, and Phosphorus

The presence of marked hypopotassemia in this case is of interest. Stamey[6] wrote that lowered values for serum potassium are noted frequently after ureterosigmoidostomy. He has shown that loss of potassium occurs from excessive renal excretion and increased diffusion from the colonic membrane into the intestine. This constant infusion of sodium and chloride ions into the extracellular fluid produces intracellular dehydration with the passage of potassium ions across the cell membrane into the extracellular space. As the result of a constant hypertonic state of the extracellular fluid, persistant polyuria develops which washes out large quantities of potassium. Experimental studies by D'Agostino, Leadbetter, and Schwartz[7] have shown that chronic depletion of potassium does take place after ureterosigmoidostomy by way of a secretory exchange with the fluid contents of the lumen of the intestine.

Although in our case the mechanisms involved in the development of hyperchloremia and hypopotassemia seem to be understood, the presence of hypocalcemia and hypophosphatemia is difficult to explain. Albright and associates[8] have described a syndrome of osteomalacia with hyperchloremic acidosis in which the basic defect was considered to be tubular insufficiency without glomerular insufficiency. In their syndrome a selective tubular defect resulted in renal inability to produce ammonia and an acid urine. Chronic hyperchloremic acidosis also developed and was followed by radiologic and chemical signs of osteomalacia. Albright postulated that the changes in calcium phosphorus resulted from the utilization of calcium as a base to combine with the excess acid. Prolonged lowering of the serum calcium produces an increased output of parathyroid hormone, with subsequent lowering of the content of phosphorus in the serum, and, finally, the prolonged excessive excretion of calcium resulted in the development of rickets in the young and osteomalacia in the adult.

Although Albright's theory of calcium loss is a logical explanation for the changes in concentration of calcium and phosphorus in the serum in this case, confusing features still remain. For example, if serum calcium is used as a base, to be excreted with chloride, it is difficult to explain why sodium is not lost also. The values for serum sodium in this patient have always been normal, suggesting that the excretion of sodium probably is not excessive. Yet therapy consisted primarily of the giving of large quantities of sodium ions to a patient in whom values for sodium were normal. With correction of the acidosis the content of sodium in the serum remained unchanged. This represents a most unusual and unexplained situation. Apparently, a

clear understanding of calcium loss in this patient is not available.

The development of acidosis was first noted in this patient 4 years after ureterosigmoidostomy. Acidosis at this time probably was not chronic, since a determination of carbon dioxide-combining power done a year later gave close to a normal value. The first evidence of chronic acidosis was recorded seven years after operation, and it was at this time that small amounts of Scholl's solution were prescribed. All laboratory and clinical evidence available since that time suggests that the acidosis had become chronic and progressive in severity.

The first determination of serum potassium was not obtained until eight years after ureterosigmoidostomy. At this time the value for potassium was recorded as being less than normal. A year later the value for potassium was found to be critical. When hypopotassemia first developed is not known, but it seems reasonable to assume that lowered levels did not develop until the onset of chronic acidosis. It is of interest to notice that all values for potassium since the initial determination have been less than normal.

Rickets and Renal Destruction

The onset of lowered values for serum calcium also is unknown, since no determinations were done until the present admission of the patient. Probably loss of calcium began when the acidosis reached a critical and sustained low level. The onset of rickets followed this loss of calcium, but the rapidity of the development of the loss of calcium cannot be determined.

The marked elevation of values for nonprotein nitrogen recorded in this patient would suggest the presence of chronic renal insufficiency. However, the reduction of these values to near normal after fluid therapy would indicate that dehydration was a significant factor. Moreover, studies by Stamey in which urine enemas were administered to normal persons suggest that there is a significant absorption of nonprotein nitrogen products by the colonic membrane. The presence of hypophosphatemia indicates that the glomerular function probably is near normal, and the presence of an albuminuria of Grade +1 in the single specimen of urine further substantiates this.

The intravenous pyelograms showed unequivocal evidence of hydronephrosis in an advanced stage. Although advanced renal destruction had occurred as a result of recurrent infections, there apparently was enough remaining parenchyma to provide near-normal function.

Treatment

Therapy initially consisted of the parenteral administration of M/6 lactate solution and later the oral administration of Scholl's solution and Potassium Triplex. With the correction of the acidosis the loss of calcium apparently stopped. The oral administration of calcium and vitamin D brought about rapid replacement of bone calcium. Within 60 days the value for serum calcium, phosphorus, and alkaline phosphatase had returned to normal and radiologically the bones appeared to have become almost completely recalcified. This response to therapy suggests that calcium and phosphorus metabolism was essentially normal and that the changes which occurred were secondary to the development of the chronic acidosis.

Summary

A case in which juvenile rickets was associated with long-standing hydronephrosis and hyperchloremic acidosis arising after ureterosigmoidostomy is presented.

Possible mechanisms in the development of the rickets are discussed. The rapid response, both clinically and radiologically, to treatment is described.

Dr. William Parson, Professor of Medicine, University of Virginia School of Medicine, Charlottesville, gave suggestions and help in preparing the original manuscript.

Miss Hazel Johnson provided technical assistance.

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Infection with Atypical Tubercle Bacilli in Graphite Pneumoconiosis

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Graphite pneumoconiosis is apparently a very rare disease in the United States, but it has been reported from other countries. Seven cases have been studied at autopsy,[1-5] and only one of these was complicated with tuberculosis.[5] The following patient was of interest, not only because he acquired graphite pneumoconiosis as a miner in this country but because he was subjected to pulmonary lobectomy for an infection with atypical tubercle bacilli. These organisms were classified with nonchromogenic mycobacteria, those which are not ordinary human pathogens. Infections with similar organisms as well as with atypical photochromogenic acid-fast organisms have been reported in association with silicosis.[6-8]

Report of Case

A 52-year-old white man was admitted to the National Jewish Hospital on June 19, 1954. He had worked in a graphite mine in Texas for nine years between 1919 and 1928. Mining was done by the dry process for two years and thereafter by the wet method. He developed a spontaneous right pneumothorax in February, 1945, which was followed by pleural effusion. Recovery ensued during sulfonamide and penicillin treatment. Tuberculosis was diagnosed in January, 1946. A two-stage thoracoplasty was performed, and he was discharged in June, 1946. He worked from then until June, 1954, when he had a slight hemoptysis. At that time he received streptomycin, isoniazid, and aminosalicylic acid for two weeks before admission to this hospital.

His symptoms were a slightly productive morning cough and exertional dyspnea. Physical examination revealed an old right-sided thoracoplasty and increased anteroposterior diameter of the chest. Rales were heard in the right upper hemithorax. Acid-fast bacilli were found in smears of concentrated sputum.

X-rays of the chest disclosed considerable peribronchial fibrous infiltration, which the radiologist considered to be suggestive of pneumoconiosis. There was some consolidation of the right hilus, and a small cavity was present in the right sixth intercostal space posteriorly. Vital capacity was 3.14 liters, or 68% of predicted normal. Maximum breathing capacity was 58 liters, or 61% of predicted normal. Arterial oxygen saturation at rest was 90% (normal: 93%). The skin reaction to old tuberculin 1:1,000 was 1+. Prior to surgery, he was treated with streptomycin (2 gm. daily for 7 days and 1 gm. daily for 21 days) combined with isoniazid (8 mg. per kilogram per day). The latter drug was continued in the dosage mentioned until after his discharge. On Jan. 19, 1955, the right upper lobe was resected. Recovery was uneventful, and he was discharged, sputum negative, in April, 1955. A recent follow-up report indicated that he is still well.

Surgical Specimen.—The right upper lobe measured 11×7×2.5 cm. and weighed 130 gm. The parenchyma was diffusely indurated and had a peculiar dark slate-gray color. A cavity measuring 3.5×2 cm. occupied the posterior segment. The lining was shaggy and trabeculated. The lumen contained some necrotic material and a 5 mm. calculus, and it communicated with a bronchus. Microscopically, the cavity contained caseous material with particles of graphite (Fig. 1) and the lining consisted of typically tuberculous granulation tissue. Many small oval confluent patches and linear streaks of nontuberculous collagenic tissue rich in fibroblasts, mononuclear cells, and some multinucleated giant cells were observed in the perifocal zone and throughout the periphery of the lobe (Fig. 2). A rare asteroid body was seen. Large amounts of black pigment in the form of angular, plate-like, needle-like, and granular particles were present in this fibrous tissue. This pigment was much coarser than the intermixed anthracotic dust. The nodular pigmented lesions often expanded the adventitia of

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Fig. 1.—Particles of graphite pigment in caseous tissue of cavity. Hematoxylin and eosin; × 475.

muscular arteries, which had sclerotic intima. The fibrosis was unaccompanied by necrosis or hyaline nodules. Hemosiderosis was diffuse and severe. The bronchial lymph nodes exhibited medullary fibrosis with minute foci of hyaline sclerosis and little graphite.

Bacteriology.—Acid-fast bacilli were cultured from the sputum on admission to the hospital and directly from the resected pulmonary cavity. On oleic acid-albumin agar[9] at 37 C the colonies were round, white, and glistening. The colonies, after exposure to daylight, became slightly wrinkled and cream-colored, but not yellow. They were strongly catalase-positive, rapidly decomposing hydrogen peroxide. The organisms were nonpathogenic for guinea pigs, mice, chickens, and rabbits. They were, from the outset, completely resistant to 20γg. of streptomycin per milliliter

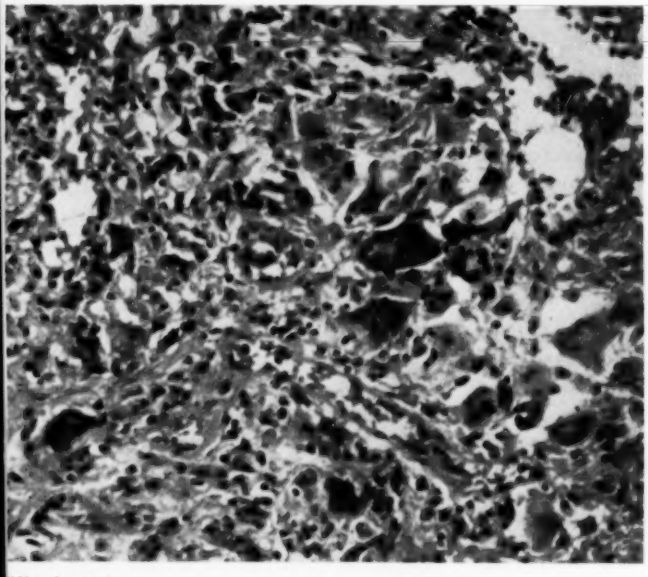

Fig. 2.—Fibrous tissue with mononuclear cells, giant cells, and graphite pigment. Hematoxylin and eosin; × 235.

and to 3γg. of isoniazid per milliliter, partially resistant to 10γg. of isoniazid per milliliter, and susceptible to 2γg. of aminosalicylic acid per milliliter. Shepard [10] recently described the characteristics in tissue culture of this organism which he classified with those of the nonphotochromogenic "Battey" type. Branching of the intracellular organisms was prominent, and coccal forms were infrequent.

Comment

The acid-fast organisms which were isolated from this patient could be included neither with the photochromogenic nor the scotochromogenic mycobacteria that have been recognized in increasing numbers of human beings. These bacilli, which also have been recognized in the southeastern part of the United States, appear to belong to a third group of *nonchromogenic mycobacteria*, a rather heterogeneous and ill-defined assemblage. All of these atypical acid-fast organisms have in common the characteristic that they are not pathogenic for those species which are usually susceptible to infection with human tubercle bacilli. (Photochromogenic mycobacteria, however, show definite pathogenicity for mice.) They are readily distinguished from typical tubercle bacilli by several cultural characteristics, including differences in colony morphology, rapid initiation of growth on media with high lipid content, very high catalase activity, and abnormal resistance to antimicrobial agents. The atypical organisms tend to be pleomorphic, varying in appearance with the composition of the medium, and they sometimes show branched forms. Bacteria of the chromogenic groups are strikingly cross barred in young cultures grown on media containing fatty acids.

The morphology of the cavity in this case was typically tuberculous. The quality of the granulation tissue which had formed throughout the lobe in response to the graphite dust was identical with that described in previous reports, although the amount of pigmentation appeared to be somewhat less. Harding and Oliver [2] demonstrated that this form of pneumoconiosis was not harmless, as previously supposed, but was a serious disabling or fatal disease. They considered that silica played a part in the pathogenesis and that the disease was an anthracosilicosis similar to that of coal workers. Jaffé,[4] on the contrary, concluded as a result of analysis of his material for silica that the tissue changes were due to the graphite.

It is noteworthy that in five of the seven recorded autopsies pulmonary cavities were present. Cavity formation was attributed to vascular obstruction and necrosis. In one of Güttner's cases,[5] both nontuberculous and typically tuberculous cavities and nodules coexisted; tubercle bacilli had been found in the sputum two months before death. The cultural characteristics of the organism were not reported.

We believe that the pneumoconiosis in our case had predisposed to the infection with mycobacteria. Crow et al.,[11] who recorded 64 cases with differing strains of nonchromogenic acid-fast bacilli, suggested that the role of previous nontuberculous lung disease in possibly preparing the ground for infection with such organisms requires more study. This case may be compared to that of Feldman and associates,[6] who described an unusual Mycobacterium which was recovered from a silicotic patient; most of the colonies were nonchromogenic, while others were yellow. They concluded that the silicosis conceivably may have provided a favorable threshold for the parasitism of an organism ordinarily nonpathogenic for man. More recently, Dworski et al.[7] published a case of far advanced silicotuberculosis with nonphotochromogenic acid-fast bacilli. Schepers et al.[8] described progressive bilateral cavitary tuberculosis caused by atypical photochromogenic bacteria in association with silicosis. They also indicated that the presence of silicosis might permit the development of a fatal infection with otherwise avirulent acid-fast bacilli. However, we have not observed evidence of silicosis in any of 11 patients with pulmonary resections for disease due to photochromogenic "yellow

bacilli"; in two of these significant anthracotic scarring was present.

It does seem reasonable to assume that, in some patients, at least, abnormal local conditions have allowed these bacteria to proliferate and to provoke tissue responses. The mechanism of the lowering of the resistance of the pulmonary tissue to infection is uncertain. The obstruction of vessels accompanying pneumoconiosis has been considered significant. The possibility that excessive lipoids in the lung might enhance the multiplication of bacteria which require them was not substantiated in this case. The scarlet R stain did not reveal neutral fat in the granulation tissue, although some was present in necrotic material of the cavity.

Summary

A patient with graphite pneumoconiosis complicated with typical cavitary tuberculosis caused by an atypical nonchromogenic Mycobacterium was described. This appears to be the second case of tuberculosis in the graphite lung and the first to be subjected to resection. This type of pneumoconiosis was considered to be a factor predisposing to progressive infection with organisms which are not ordinarily pathogenic for man.

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Hyperthyroidism and Parkinsonism

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The correlations between hyperthyroidism and Parkinsonism have been excellently covered in a recent paper in this journal.[1] The following observations may serve as a modest complement.

Firstly, there is a syndrome, mostly encountered in young women, which at the surface is extremely suggestive of hyperthyroidism: they have exophthalmus, anxiety, restlessness, tachycardia, and tremor. The real cause of this syndrome is encephalitis, and it is, as a matter of fact, rather easy to distinguish the syndrome from hyperthyroidism: 1. The tremor is rather more coarse than in hyperthyroidism. 2. The basal metabolic rate is decreased, say to −20% or −30%. 3. There is a pleocytosis in the cerebrospinal fluid. I have personally observed this syndrome repeatedly and more often than not have these patients been interpreted by the general practitioner as hyperthyroidism. Why the syndrome is especially apt to occur in young women I cannot say.

Secondly, the time-honored belief in hyperthyroidism as induced by fear (the German "Schreck-Basedow"), has to some extent been substantiated by observations during the last big war. A distinguished British colleague has told me his impression of being surrounded by severe cases of hyperthyroidism when in the early morning he entered a military hospital established in a church at the southern coast of England. During the night there had arrived soldiers, carried across the canal during the famous evacuation of Dunkerque, all of whom had a pronounced exophthalmus, tachycardia, and restlessness. Hypnotics and sleep for 24 hours were sufficient to bring about a complete recovery. I have witnessed the same during the "winter war" between Finland and Russia in 1939-1940. At the northern front, in Lapland, the relationship between the forces approached 1:100, to the advantage of the Russians. It was impossible for the small minority of the Finns to get any sleep whatsoever during weeks, and this, in connection with the stress of the campaign, once in a while gave the same result of a "pseudohyperthyroidism." Considering the importance of the centrencephalon for sleep and the reactions of fear entailed by many lesions of and interventions on the basal structures of the brain, it does not seem out of the way to recollect these observations.

Finally, the following observation of mine seems to give food for thought.

Report of Case

A man in his 50's applied for medical assistance because of a full-blown syndrome of Parkinsonism. When his medical history was scrutinized, it turned out that he had had hyperthyroidism some 10 years ago. For this he was treated by a most able and competent physician with iodine. Being of a conscientious mind and fearing to get the hyperthyroidism back, he continued his medication with iodine, on his own account, for all the subsequent years. I felt that this was going a bit too far, so I made him discontinue his use of iodine; otherwise he just got a small dosage of scopolamine. In about one month he reappeared; all symptoms of Parkinsonism had disappeared, and he was very content, only a bit anxious lest the hyperthyroidism should reappear. Reassured on this point, he returned home; after some few weeks he thought he felt some tachycardia, and imagining that the hyperthyroidism had returned he again took to iodine in the old, rather substantial dose. He reappeared after about one month, and his old symptoms of Parkinsonism were again to be registered. As for the scopolamine, he had continued this medication all the time through. Again I made

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him discard the use of iodine, and again the same sequence of events appeared: The symptoms of Parkinsonism disappeared, he again took to iodine and the symptoms returned. This was repeated at least once more, then I lost sight of the patient. Yet, at three various occasions the use of a substantial dose of iodine for a long time induced the symptoms of Parkinsonism.

Summary

Attention is called to the appearance in young women of a syndrome which at the bedside may closely imitate hyperthyroidism but which is due to encephalitis.

Attention is called to the syndrome of exophthalmus, tachycardia and anxiety and restlessness, to be elicited by fear while under stress.

One case is briefly described where the administration of iodine on at least three various occasions did result in a syndrome of Parkinsonism.

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Kidney, Adrenal Cortex, and Hypertension

Theory and Facts

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Each step forward in science represents a simplification. Complex and hitherto apparently unrelated phenomena begin to fall into place after the development of an idea or hypothesis. The nearer a causal chain approaches to the final event, the more influential do individual factors seem to be until, when we reach the terminal stage, the causal agent seems to be in unique relationship with the ultimate effect.

G. W. Pickering
"High Blood Pressure"

Ever since Johnson (1868) advanced the conception that hypertension results from the contraction of the arterioles throughout the body there has been ceaseless clinical and experimental investigation aimed at the detection of the factors responsible for arteriolar constriction in hypertension. Although Johnson's teleological explanation is untenable nowadays, the conception that hypertension is produced by functional vasoconstriction has steadily gained ground and is now universally accepted.

Two main factors have been considered in the mechanism of arteriolar constriction for almost a century: neurogenic and humoral. It has been known since the time of Claude Bernard (1851) that stimulation of the sympathetic nerves usually produces vasoconstriction (except in the heart), the intensity of the effect varying from one organ to another. Cutting the sympathetic or temporarily interrupting it by local anesthesia increases the blood flow through the affected tissues (other than brain and kidney). When we add to these facts the usual pressor response to disturbing emotions it does not seem surprising that a nervous pathogenesis has been considered from the earliest studies of essential hypertension. As long ago as 1855, Rokitansky, the morphological pathologist par excellence, attributed idiopathic cardiac hypertrophy, doubtless predominantly our essential hypertension, to a disturbance of innervation. Laycock, another early student, suggested in 1873 that Bright's disease results from primary disease of the nervous system. With the establishment of unequivocal evidence that increased peripheral resistance is the immediate mechanism of the rise in blood pressure, the line of thought that neurogenic factors contribute directly to increased vascular resistance in hypertension was rendered all the more appealing.

Nevertheless, the increasing efficiency and precision in experimental medicine has begun to throw more light on the pathogenesis of hypertension, strongly supporting partisans of the "humoral" etiology of this disease. There is now very conclusive evidence that constriction of the renal artery initiates hypertension through a change in the chemical composition of the blood. This is indicated by the fact that denervation of the kidneys and sympathectomy do not interfere with the experimental hypertension obtained by clamping of the renal artery (Page [1935] and Collins [1936]). Likewise speaking unequivocally for a chemical mechanism of hypertension is the production of elevation of blood pressure by constric-

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tion of the artery of a kidney transplanted to the neck of dog, when the nervous connections of the kidney are beyond doubt severed (Blalock and Levy [1937] and Glenn, Child and Heuer [1937]). Furthermore, section of the splanchnic nerves on both sides (Goldblatt et al. [1937]) or of the sixth thoracic to the second lumbar anterior spinal nerve roots (Goldblatt and Wartman [1937] and Page [1938]) does not prevent the elevation of blood pressure. Finally, complete removal of the sympathetic chains and cardiac denervation likewise neither prevent the development of hypertension nor abolish it (Freeman and Page [1937], Alpert et al. [1937], and Heymans et al. [1937]). All of these findings are most convincing that, at least in the experimental hypertension, the kidney initiates elevation of the blood pressure through a humoral mechanism.

Various vasoconstrictive substances, found in the body fluids of hypertensive patients, have been described. In 1904, Elliot noted the similarities between the effect of stimulation of the sympathetic nerves and that of epinephrine. It was suggested that the autonomic nerves might produce their effects by releasing at their terminations chemical substances with specific affinity to the receptors of the motor units activated. The classical works of Dale (1933) and von Euler (1951*a*) resulted in the isolation of these substances and their identification as epinephrine and norepinephrine (arterenol), both of which have been shown to be secreted by the adrenal medulla. Although norepinephrine has a fairly generalized constrictor effect on blood vessels, consistently raising the peripheral resistance, increased amounts of this amine have been found only in patients with pheochromocytoma (von Euler [1951*b*]). It is now an accepted fact that neither norepinephrine nor epinephrine, nor other sympathicomimetic amines, bear any direct relationship to arterial hypertension other than that found in cases with adrenal medullary tumor. Nevertheless, these findings gave rise to a constantly increasing interest in the adrenal glands as an important, if not causative, factor in arterial hypertension and stimulated an intensive search for other humoral agents which could be responsible for the increased vascular resistance. The central point of subsequent investigations has been shifted from the adrenal medulla to the adrenal cortex.

In 1937, Goldblatt made his outstanding discovery that bilateral adrenalectomy interfered with the development or maintenance of experimental hypertension in animals. Similar reports were subsequently published by Blalock and Levy (1937), Page (1938), Collins and Wood (1938), Enger et al. (1938), Diaz and Levy (1939), Williams et al. (1939), Friedman et al. (1940), Remington et al. (1941), Dell'Oro (1942), Houssay and Dexter (1942), Braun-Menendez and Foglia (1944), Guadino (1944), and others.

In his experiments Goldblatt (1934, 1937, and 1948) produced hypertension by clamping the renal artery, thus reducing the renal blood flow. It is convenient at this point to recall the events which formed the present conception of the role of kidney in the elevation of arterial blood pressure.

In 1827, Richard Bright described his observations on the association of cardiac enlargement with diseased kidneys. Nine years later (1836), he gave his ingenious explanation of the noted changes:

> The deviations from health in the heart are well worthy of observation: they have been so frequent, as to show a most important and intimate connection with the disease of which we are treating. . . . The obvious structural changes in the heart have consisted chiefly of hypertrophy. . . . This naturally leads us to look for some less local cause, for the unusual efforts to which the heart has been impelled, and the two most ready solutions appear to be, either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately, or, that it so affects the minute and capillary circulation, as to render greater action necessary to force the blood through the distant sub-divisions of the vascular system.

The invention of the sphygmomanometer made possible the discovery that an elevated arterial pressure was a constant finding in Bright's disease and was the cause of the cardiac hypertrophy. Thus high blood pres-

sure resulting from renal disorders gained the label "renal hypertension," as opposed to "essential hypertension" in which the renal function is primarily unimpaired and the etiology unknown. The fact of the existence of hypertension caused by renal disease stimulated the search for hypertensive agents within the kidney.

In 1898, long before Goldblatt's experiments, Tigerstedt and Bergmann demonstrated in anesthetized rabbits that a prolonged rise in arterial pressure is obtained by the intravenous injection of saline extracts of fresh rabbit kidneys or of the residue left by extracting kidneys with alcohol. They named the active substance renin and were able to give a correct description of its properties, its distribution in the kidney, and the potentiation of its effect by nephrectomy. Although Tigerstedt and Bergmann's findings were confirmed by Bingel and collaborators (1909, 1910), renin began to evoke a real interest of investigators only with the publication of works by Pickering and Prinzmetal (1938) and Landis et al. (1938).

Thanks to the work of Page (1939) and Braun-Menendez and their collaborators (1944, 1946), it is now known that renin does not itself cause vasoconstriction. It acts enzymatically on hypertensinogen, one of the α_2-globulins of plasma, splitting off a smaller molecule which exercises a pronounced vasoconstrictive effect. This substance is probably a polypeptide and has been named hypertensin, or angiotonin. Its action may be prevented by the enzyme hypertensinase, which destroys hypertensin (Bean [1942] and Sapirstein et al. [1944]). This enzyme is present abundantly in various tissues and in smaller amounts in plasma. It has been suggested by Pickering (1945) and Ogden (1947) that the renin-angiotonin mechanism functions in the first days of experimental renal hypertension but that after this the high blood pressure is sustained by an extrarenal mechanism. This concept is based on their findings that during the first days of experimental renal hypertension the elevated arterial pressure is abolished by nephrectomy and the kidney contains no excess of renin.

These findings contributed to a widening of the horizons and evoked a renewed interest in the search for an extrarenal pressor factor.

Meanwhile Shorr and his collaborators (1945 and 1948) described new vasotropic principles of renal and hepatic origin: vasoexcitor material (VEM), formed by the kidney, and vasodepressor material (VDM), produced by the liver. Both of them are produced only under anaerobic conditions and are not directly vasoconstrictor or vasodilator but act by increasing and decreasing, respectively, the sensitivity of the terminal arterioles to epinephrine. Shorr adduced evidence that displacement of the equilibrium between VEM and VDM may be concerned in the pathogenesis of both low and high blood pressure. Adrenalectomy was shown to abolish the capacity of the kidney to form the vasoexcitor material even in animals maintained on high-salt diets (Zweifach et al. [1947]). Although these findings do not seem to add much to our understanding of the mechanism of hypertension, they have stressed the dependence of the role of the kidney in the regulation of blood pressure on an extrarenal mechanism and pointed once more to the adrenals as a *sine qua non* in the production of experimental hypertension.

When Goldblatt demonstrated in 1937 that bilateral adrenalectomy prevented the development of hypertension and that this effect was due to the removal of cortical but not medullary tissue, many facts were already known from clinical experience, which indicated a possibility that the adrenal cortex might be involved in the mechanism of hypertension. The first description of hypertensive changes secondary to an adrenocortical tumor had been reported in 1897 by Neusser, and a further hint of a possible relationship between the adrenal glands and hypertension was made by Josué, in 1903. Little notice, however, was given to this association until the more extensive

observations of Oppenheimer and Fishberg, in 1924.

In 1932, Cushing described a clinical syndrome which he thought was due to basophil adenoma of the pituitary gland. Hypertension was one of the cardinal features of this syndrome. Subsequent work has shown that the factor responsible for the disturbances described by Cushing was an increased production of adrenocortical steroids by either tumor or hyperplasia of the adrenal cortex. Various authors commented upon the elevated blood pressure in patients with adrenocortical tumors or hypertrophy and contrasted it with the reduced blood pressure of Addison's disease (1855), in which "cortical atrophy" was found to be responsible for the signs and symptoms, including the arterial hypotension invariably accompanying this disease.

It is now well known that the elevation of blood pressure in Cushing's syndrome is the effect of an increased production of corticoids whereas the low pressure in Addison's disease is due to adrenocortical hypofunction. In 1939, Loeb and his colleagues called attention to two patients with Addison's disease whose arterial pressure exceeded normal limits in the course of treatment with deoxycorticosterone. Since then an impressive body of evidence has accumulated, which strongly suggests that the adrenal cortex plays an important role in maintaining arteriolar tonus and is directly or indirectly involved in the mechanism of hypertension.

Perera (1945) reported that in a hypertensive patient who developed Addison's disease the blood pressure fell to subnormal levels. Hypertension was restored by administration of steroids, but replacement therapy with salt alone resulted in a drop in blood pressure to normal limits, even though the patient was maintained in water and electrolyte balance. "One could not help but conclude that the adrenal cortex or appropriate steroid substitution therapy was important for the development or maintenance of this man's essential hypertension" (Perera). This was confirmed by Thorn et al. (1952), who also reported a fall of blood pressure to normal level in a hypertensive patient who developed Addison's disease.

Recently Conn (1955) described a new clinical entity, "primary aldosteronism," a syndrome due to adrenocortical tumor secreting increased amounts of the sodium-retaining hormone, in which one of the cardinal features is hypertension.

During the last two decades countless experiments on animals have proved that the adrenal cortex plays an essential part in hypertension. In his pioneer investigations, Goldblatt (1937) showed that, while the elimination of both adrenal medullas does not interfere with the production of hypertension by constriction of the renal artery in dogs, the blood pressure falls to normal after bilateral adrenalectomy. However, the hypertension could be restored by administration of cortical extracts, dehydrocorticosterone, or deoxycorticosterone acetate (DOCA) (Page and Lewis [1951]). Moreover, doses of cortical extract or cortisone, equal to the amount that maintains hypertension in adrenalectomized dogs or rats, did not raise the blood pressure in normal animals. Adrenalectomy also interfered with the development or maintenance of hypertension produced in animals by various procedures other than clamping the renal artery; Jeffers et al. (1937) demonstrated this in experimental hypertension produced by the intracisternal injection of kaolin in dogs; Page and Reed (1945), in hypertension evoked with dehydroxyphenylalanine and related compounds in rats; McCann et al. (1948), in hypertension obtained by auditory stimulation in rats. The importance of the presence of functioning adrenocortical tissue for the development or maintenance of high arterial pressure was also shown in renoprival * hypertension. Brilliant experiments were performed on single and parabiotic rats by Ledingham (1951) and Floyer (1951). The results of these experiments are summarized by Wilson (1953):

* Hypertension which occurs after bilateral total nephrectomy.

Total nephrectomy in single rats (maintained with peritoneal lavage) results in hypertension. If the adrenals and kidneys are removed together, this rise does not occur. The parabiotic preparation is more suitable for such experiment than the single rat. Bilateral nephrectomy in one member causes hypertension in that member but not in its partner with intact kidneys. Removal of both adrenals in the nephrectomized, hypertensive member results in a prompt fall in blood pressure to the normal level. Implantation of deoxycortone acetate will cause the blood pressure to rise again in this preparation. (Wilson [1953]).

Moreover, some workers (Williams et al. [1939], Friedman et al. [1940], Remington et al. [1941], Lewis and Goldblatt [1942], Dell'Oro [1942], and Houssay and Dexter [1942]) noted that adrenalectomy was associated with a fall in the blood concentration of hypertensinogen and, frequently, there was a reduced response to renin. It has also been shown by Shorr and his collaborators (1948) that adrenalectomy impairs the renal capacity to form vasoexcitor materials, under anaerobic conditions, even in animals maintained on high-salt diets. Administration of cortical extracts restored normal behavior of kidney.

The effect of adrenalectomy on hypertension in animals has been commented upon by many workers. It has been assumed that ". . . this effect can be partly accounted for by salt deficiency, the extracellular fluid being depleted of sodium, and hence of water, because of the failure of the kidneys to conserve sodium" (Pickering, "High Blood Pressure,[11] p. 75). However, a direct action of corticoids was sought by other investigators. An interesting explanation has been put forward by Ramey, Goldstein, and Levine (1951). They have demonstrated in a series of brilliantly designed experiments that a single injection of adrenal cortical extract, but not of deoxycorticosterone, would potentiate the response to norepinephrine in adrenalectomized dogs, though not in normal controls. Moreover, Fritz and Levine (1951) found that the vessels of the mesoappendix of the adrenalectomized rat became refractory to the repeated application of norepinephrine while those of the normal rat did not. The responsiveness of the vessels was restored by 11-oxysteroids injected intramuscularly or applied locally in much smaller doses. They conclude that these corticoids are necessary to obtain the optimal response of the blood vessels to norepinephrine (Sympathin E).

The elevation of blood pressure following the administration of various steroids has been reported by many workers. Selye and his co-workers (1943), were the first to describe morphological changes in various organs of several animal species caused by massive doses of deoxycorticosterone acetate and salt. These changes consisted of widespread vascular lesions—similar to those seen in human nephrosclerosis and in the accelerated phases of essential hypertension—cardiac hypertrophy, and a decrease in adrenal size. Subsequent studies by Knowlton and his collaborators (1946), employing much lower dosages in rats, revealed no significant vascular lesions but some degree of cardiac and renal enlargement, even in the absence of hypertension. Selye (1946) noted that the degree of pathological response to deoxycorticosterone acetate was intensified by an increase in sodium chloride in the diet or by preliminary excision of one kidney. Also Knowlton and associates (1947) demonstrated that the hypertensive action of this steroid was potentiated by salt. Friedman and Friedman (1949) noted that the hypertension caused in rats by deoxycorticosterone acetate was paralleled by hypertrophy of the kidney. In mice, injections of adrenocorticotropic hormone was reported to be followed by hypertrophy of the juxtaglomerular apparatus, but there was no evidence of hypertension in the weight of heart (Dougherty [1948]). Finally Friedman et al. (1952 and 1953), in a screening test for renal and cardiovascular effects of different adrenal hormones in rats, demonstrated that hydrocortisone had the most pronounced hypertensive effect of all the corticoids tested. They suggested that this steroid might exercise a direct action on the vascular bed, in contrast to deoxycorticosterone acetate.

In man, the administration of various adrenocortical hormones causes likewise an elevation of arterial pressure. The story begins with the theory advanced by Ambard and Beauyard (1905) that hypertension results from the retention of sodium chloride in the organism. They observed that the blood pressure of hypertensive persons is elevated by the ingestion of salt and lowered by the elimination of salt from the diet. In more recent years, Allen and Sherrill (1922) and others (Volhard [1931], Kempner [1946 and 1949], and Corcoran et al. [1951]) have succeeded in markedly lowering the blood pressure in many patients with hypertension by a salt-poor diet. Perera and Blood (1946) found that the hypertensive patient is more resistant than the normal to the dehydrating effect of salt restriction. Many investigations concerned with electrolyte metabolism have been carried out by various workers. The findings suggest that sodium retention favors a rise in blood pressure, but there does not appear to be evidence that sodium retention is primarily concerned in the pathogenesis of human essential hypertension.

With the detection of the electrolyte-regulating properties of certain corticoids the central point of the investigations concerned with a possibility of disturbance of the salt metabolism in hypertension was transferred directly to the adrenal cortex. As already mentioned, Loeb et al. (1939) first reported hypertension in two patients suffering from Addison's disease, who were treated with deoxycorticosterone esters. Reports of Thorn and Firor (1940) and McCullagh and Ryan (1940) confirmed that a considerable rise of pressure, even to hypertensive levels, might result from the administration of large doses of cortical extracts or deoxycorticosterone acetate and salt to patients with Addison's disease. This pressor effect has also been demonstrated in uncomplicated hypertensive vascular disease but not in normotensive subjects (Perera and Blood [1947]). The prompt rise in blood pressure in the hypertensive group could not be ascribed to salt and water retention, as there were similar changes in the normal group. Finally, since the introduction of cortisone and hydrocortisone to wide clinical use, it has been well known that overdosage or prolonged treatment with these drugs frequently results in an elevation of arterial blood pressure, which returns to normal on withdrawal of the drug or reduction of its dosage (first reported by Hench, Kendall, Slocumb, and Polley [1949]).

Corticotropin (ACTH) was also shown to elevate arterial blood pressure. Perera (1950) confirmed the report of Hench and his associates (1949) that adrenocorticotrophic hormone may raise the blood pressure of nonhypertensive patients. In hypertensives it causes a marked increase in arterial tension and exacerbation of signs and symptoms and frequently precipitates crises of hypertensive encephalopathy. (This was demonstrated to be definitely not due to increase in circulating epinephrine or norepinephrine.) These observations of the pressor action of corticotropin were subsequently confirmed by many clinical reports.

All these findings built up a rationale for the introduction of bilateral adrenalectomy as a surgical procedure in the treatment of severe hypertension. As far back as 1914, Crile (1938) combined unilateral adrenalectomy with ligation of the thyroid arteries and cervical sympathectomy in an operation for hypertensive disease. Subsequently, DeCourcy et al. (1934), Allen and Adson (1937), and Neuhof (1948) performed partial or subtotal adrenalectomies together with other surgical procedures in patients with severe essential hypertension. However, total adrenalectomy became feasible only with the introduction of cortisone for clinical use. Since then many reports of total or subtotal adrenalectomy for hypertension have appeared, but it is difficult to assess its value, as it was combined with various types of other surgical procedures, mainly with sympathectomy. Green and his associates (1950) were the first to describe a patient with malignant hypertension and diabetes mellitus whom they treated by total

adrenalectomy alone. The operation was followed by a fall in blood pressure and a dramatic remission of the diabetes, this still continuing 15 months after adrenalectomy. In 1952, Thorn et al. described the effect of total adrenalectomy alone in the treatment of high blood pressure in 10 patients with severe essential hypertension and in 5 with chronic glomerulonephritis. Wolferth described, in 1953, the results of subtotal and total adrenalectomies in hypertensive patients; however, adrenalectomy alone was performed only in two patients of his series, various types of sympathectomy being combined with the adrenalectomy in the others. Bowers (1954) described the response to partial adrenalectomy in a series of 26 patients with essential hypertension. In Britain, Pickering, Wright, and Heptinstall (1952) were the first to record their experience of partial adrenalectomy for hypertension in children with pyelonephritis. Rosenheim (1954) described the effects of total adrenalectomy in two patients with hypertension, one of whom had the malignant type. Finally, Wilson (1955) reported the effect of total bilateral adrenalectomy in a patient with carcinoma of the prostate who had benign essential hypertension. However, in most of these studies the data are not sufficient to assess accurately the effect of adrenalectomy on the hypertensive state. The most comprehensive study is that by Thorn et al. (1952), but there is a relative lack of sufficient information about the patients' conditions during the follow-up period. Only the recent work by Arnott, Crooke, Donovan, and Taylor (1957) furnishes more comprehensive and valuable information about the patients' condition during a long postoperative period and gives a detailed account of the electrolyte balance in the patients studied. In the light of the conclusive evidence supplied by this investigation, the results of previous workers can be reassessed and better understood. It seems established now that in patients with severe hypertension who have had bilateral adrenalectomy blood pressure can be maintained at normal levels if the daily cortisone dose is low enough to keep the patients in a state of mild "adrenocortical hypofunction." The authors conclude:

It is clear that the vascular disease has been retarded or, perhaps, even arrested by a state of slight adrenocortical insufficiency but it appears that the liability to excessive constriction of the arteriolar vascular bed, which is fundamental to essential hypertension, persists and that a slight increase in the dosage of cortisone quickly recalls a severe hypertensive state.

In the light of all the facts and findings described above, it seems to be proved beyond any doubt that the adrenal cortex plays an essential part in the development and maintenance of arterial hypertension. The exact nature of this relationship, however, and the way in which adrenocortical secretion influences the mechanism of high blood pressure has not been as yet elucidated. All the evidence derived to date from clinical and experimental trials provokes two alternative assumptions:

1. The role of the adrenal cortex in hypertension is of a merely "permissive" † nature. This is to be understood as follows: Adrenocortical secretion, or more precisely its mineralocorticoid part, is essential for the maintenance of the proper Na^+ and K^+ intracellular concentrations; these concentrations are responsible for the general muscular tonus, including that of the vascular musculature, thus conditioning the response of the arterioles to various vasoconstrictive agents.

2. Adrenocortical hormones per se contribute directly to the increased (and normal) vascular resistance, either acting as pharmacodynamically active compounds on nerve endings in the arteriolar wall (or on the muscle directly) or increasing the responsiveness of the arterioles to norepinephrine or other vasoconstrictive substances.

Attempts have been made by various workers to approach the problem more directly by investigating the possibility of increased secretion or an altered pattern of secretion

† The term "permissive action" was first used by Ingle (1943) to illustrate the relationship of the adrenal cortex to the diabetogenic effect of estrogen.

of adrenocortical steroids in hypertension. All this is relatively new work, as methods for the estimation of various corticoids in blood and urine have been developed only recently.

Bruger, Rosenkrantz, and Lowenstein were the first (1944) to estimate the 17-ketosteroid excretion in urine (24-hour specimens), with use of a method based on the Zimmerman color reaction. They selected only female subjects for their investigation, in an attempt to eliminate the androgenic steroids of testicular origin contributing to the color produced with the Zimmerman reagent. Fourteen normotensive and forty hypertensive subjects were investigated. The urinary excretion of the 17-ketosteroids was found to be significantly lower in the hypertensive group, although it was still within the lower limit of the excretion of the normal subjects. The authors' suggestion, that these findings may indicate an altered pattern of corticoid production or a hypofunction of adrenal cortex due to exhaustion under the constant strain imposed upon it by the persistent elevation in blood pressure, does not seem convincing. In the same paper it is reported that no difference in the incidence of hyperplastic or adenomatous changes in the adrenal cortex between normal and hypertensive subjects could be demonstrated.

The low urinary excretion of the 17-ketosteroids was also reported by Selye (1947) in 12 of 18 hypertensive patients. This was accompanied by an increased glucocorticoid urinary excretion, as determined by the method of Venning et al. (1946), based on the glycogen deposition test in the liver of a fasting adrenalectomized mouse. The author remarks, "Interpretation of these data is impossible at present."

Daughaday, Jaffe, and Williams (1948) measured the urinary excretion of formaldehydogenic steroids in various endocrine and nonendocrine diseases. Three hypertensive patients were included in this study, but no difference could be demonstrated between their excretion and that of the normal subjects. The authors remark that the method presumably measures nonglycogenic as well as glycogenic steroids.

The formaldehydogenic method (Corcoran and Page [1948]) was also used by Tobian and Joseph (1949) for the estimation of the urinary corticosteroid excretion in normal subjects and patients with essential hypertension. No differences could be demonstrated in the two groups. In addition, in eight hypertensive and seven normotensive subjects plasma corticosteroid levels were estimated by the Heard-Sobel and Corcoran-Page-Lowenstein methods. Both groups exhibited similar plasma corticoid concentrations. The authors report in the same paper the results of other laboratory investigations in 46 normal subjects and 40 patients with essential hypertension. No differences could be demonstrated between the two groups in the "fasting blood" eosinophil concentration, in plasma CO_2-combining power, and in CO_2/Cl ratio in blood.

In contrast to these findings Corcoran, Page, and Dunstan (1950) reported increased levels of the urinary formaldehydogenic corticoids in 20 of 46 patients with essential and malignant hypertension. The normal range was established by investigating 30 normal subjects. The method used in this work was that developed and reported previously by the authors. This method measures only the free (unconjugated) fraction of the formaldehydogenic steroids. This is also stressed by the authors, who suggest, "The possibility arises that the increased excretions of patients with hypertension may reflect some inadequacy of corticoid conjugation. The hypercorticoiduria of hypertension would not in this case reflect an absolute hypersecretion." The higher values in these series could be, however, explained by a purely technical consideration: While in the normal subjects 12-hour urine samples were collected, the specimens from hypertensives consisted of pooled 72-hour samples. It is thus likely that some degree of spontaneous hydrolysis

of the conjugated corticoids occurred in the latter specimens.

Hetzel and Hine (1952) investigated again the urinary 17-ketosteroid excretion in hypertensive patients as well as the urinary excretion of glucocorticoids determined by biological assay. In view of the similar results obtained in normal and hypertensive subjects, the authors conclude: "There is no evidence (from this investigation) for a significant disturbance of adrenal cortical function in hypertension (except that associated with the Cushing's syndrome). It must be admitted that the techniques available for the determination of adrenal cortical function are by no means as precise as could be desired."

A study by Genest (1954) was undertaken with a view to investigating the relationship between sodium, arterial hypertension, and the adrenal glands. Seven patients with essential hypertension were studied from two to seven consecutive months under conditions of high-sodium and of low-sodium intakes. The urinary steroid excretion was determined by Archibald's chromatographic fractionation procedure (1949). The state of adaptation of the seven patients in response to a severe and prolonged restriction of sodium, whether or not accompanied by a fall in their blood pressure, was not reflected in any significant change in the excretion or pattern of the urinary steroids estimated.

In a more recent work (1956) Genest et al. suggested that hypertension might be a state of mild chronic hyperaldosteronism. However, the methods used in that investigation for estimation of the sodium-retaining hormone are very far from perfect, and the evidence presented is inconclusive.

Finally, the work by Wallace and his associates (1955) should be mentioned. These workers investigated plasma levels and urinary excretion of the 17-hydroxycorticosteroids, as measured by the Porter-Silber chromogens, in healthy persons and in patients with various diseases. A series of 19 patients with several types of renal disorders is included in this work, among them 2 patients with "accelerated phase" of hypertensive cardiovascular disease. In this series also urinary 17-ketosteroids and blood urea nitrogen were determined. The urinary corticoids were estimated after glucuronidase hydrolysis. Although the authors do not supply any clinical data, it is conceivable that most of the patients of this series exhibited an elevated blood pressure. In one case of acute glomerulonephritis, three cases of chronic glomerulonephritis, and one of the two hypertensive patients low urinary values of the 17-hydroxycorticosteroid-glucuronides and the 17-ketosteroids were found, in notable contrast to normal plasma levels of the 17-hydroxycorticosteroids. The authors remark: "In this group (of patients) the normal plasma concentrations and the clinical appearance appeared to be more indicative of the state of adrenal function than were the urinary values. . . . The explanation of these low urinary values is not as yet established."

An analysis of the methods used in all of these investigations reveals that only the "free" fraction of corticoids has been estimated in blood whereas the "total" (free and conjugated) corticoids have been measured in urine. The work of Corcoran et al. is here an exception, but these authors again estimated only the "free" corticoids in urine, which constitute merely a small fraction of the "total" urinary corticoid excretion. Furthermore, the formaldehydogenic method used in most of these investigations for the estimation of the glycogenic corticoids measures a very wide group of compounds and is not sensitive enough for the determination in blood. Finally, the determination of androgenic steroids (17-ketosteroids) in hypertension does not seem to have a strong rationale as, although they partly constitute the metabolic product of the glucocorticoids, their concentration in urine or blood hardly reflects adrenocortical activity (Sayers [1950]).

Recently work was undertaken by me (1957) with the object of reinvestigating the relationship between the adrenal cortex, kidney, and high blood pressure. A new

approach was applied to this problem by an investigation of the renal clearance of endogenous 17-hydroxycorticosteroids, free and conjugated corticoids being estimated separately. Fifteen normotensive and thirteen hypertensive patients were investigated. The results obtained indicate that the renal clearance of the conjugated 17-hydroxycorticosteroids is grossly impaired in the hypertensive patients (essential hypertension). This leads to the accumulation of the conjugated corticoids in blood, with a resulting alteration in the ratio of free to conjugated 17-hydrocorticosteroids in plasma (Kornel [1957]). Further results, obtained from experiments in which the clearance of 17-hydroxycorticosteroid-glucuronides was determined in parallel with that of the total conjugated 17-hydroxycorticosteroids and from another series of estimations when the basal clearance was compared with that on corticotropin, suggest that the decreased clearance of the conjugated 17-hydroxycorticosteroids in hypertensive persons possibly results from an altered pattern of the conjugation (Kornel [1958]). Further work is in progress.

To end this review, it is opportune to recall the words of Dr. Thomas Addison (1855) from his work, "On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules":

> . . . and however unimportant or unsatisfactory these findings may at first sight appear, I cannot but indulge the hope, that by attracting the attention and enlisting the co-operation of the Profession at large, they may lead to the subject being properly examined and sifted, and the inquiry so extended, as to suggest, at least, some interesting physiological speculations, if not still more important practical indications.

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Contributions of Basic Science to Modern Medicine

Renal Excretion of Calcium and Phosphorus

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Knowledge of the metabolism of calcium and phosphorus is of considerable importance to the internist. An understanding of the metabolic turnover of these ions is necessary in the consideration of bone diseases. Abnormalities of calcium and phosphorus metabolism are common in acute and chronic renal failure. Disturbances in neuromuscular function are frequently related to alterations in the concentration of ionized calcium in the extracellular fluid. Phosphorus is an important intracellular anion, which enters into numerous biochemical reactions.

Alterations in calcium and phosphorus metabolism are often reflected in abnormalities of urinary excretion. It is pertinent, therefore, to examine the renal mechanisms concerned with the excretion of these ions. Although the metabolism of calcium and phosphorus are commonly considered together, it will be more convenient to examine the renal excretion of these substances separately, as the mechanisms involved are very different.

Renal Excretion of Phosphorus

Normally most of the phosphorus lost from the body appears in the urine. Variation in dietary phosphorus intake or alterations in phosphorus metabolism in disease are usually accompanied by changes in renal phosphate excretion. The renal mechanisms involved in inorganic phosphate * excretion include filtration, tubular reabsorption, and possibly tubular secretion. At normal or moderately elevated plasma phosphate levels all of the inorganic phosphate is filtrable at the glomerular membrane. Thus, the amount of phosphate filtered by the glomeruli can be calculated as the product of the glomerular filtration rate and the plasma phosphate concentration. The quantity of reabsorbed phosphate is calculated as the quantity of filtered phosphate minus the quantity of excreted phosphate. In normal subjects, at endogenous plasma phosphate levels 85%-95% of the filtered phosphate is reabsorbed by the renal tubules. The absorption is predominantly (perhaps solely) a function of the proximal tubules.[1,2]

It has been shown in animals and in man[3-7] that progressive elevation of the plasma phosphate concentration results in an increased tubular reabsorption until the tubular reabsorptive mechanism becomes saturated. Further increase in plasma phosphate is not accompanied by increase in tubular reabsorption. There is a maximal rate of tubular transport (Tm) for phosphate. The relationship between filtered, reabsorbed, and excreted phosphate at various plasma phosphate levels is illustrated in Figure 1.

Since phosphate excretion is determined by the processes of filtration and reabsorp-

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Because of the large number of requests anticipated for reprints of the papers of this series, it is planned to bind them together after the last has appeared. They may be obtained for $1.00 ea. by addressing requests to Mr. Ed McNabb, Baird-Ward Printing Co., Box 539, Nashville 1, Tenn. NOTE: Enclose remittance with order.

* The term phosphate will be used in the discussion that follows to designate the inorganic phosphate ions (mono and dihydrogen phosphate) with which we are concerned.

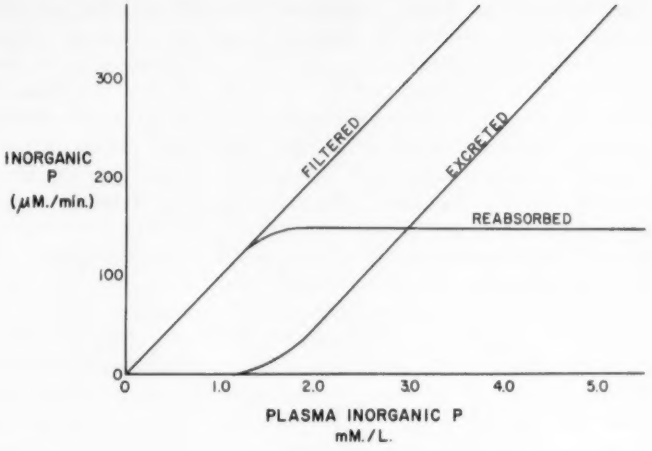

Fig. 1.—Normal relationship in man between the quantities of inorganic phosphate filtered, excreted, and reabsorbed at various plasma phosphate concentrations.

tion,† alterations in either of these functions may be expected to result in changes in phosphate excretion. Under conditions of a reasonably stable phosphate intake the normal relationship between filtration and reabsorption may be viewed as one of glomerular-tubular balance and is illustrated schematically in Figure 2. Glomerular-tubular balance implies that the processes of filtration and reabsorption function together to maintain a normal concentration of phosphate in the body fluids. Since the amount of phosphate filtered depends upon the glomerular filtration rate (GFR) and upon the plasma phosphate concentration, alterations in either of these will change the filtered load. Thus, in the discussion of

† The term reabsorption as used in this paper connotes *net* reabsorption. It is likely that the inorganic phosphate ions move across the proximal tubular epithelium in both directions, i.e., from tubular lumen to blood and from blood to tubular lumen. However, in most if not all situations in mammalian species the *net* movement of phosphate ions is from tubular lumen to tubular blood, this direction of transport being termed absorption or reabsorption.

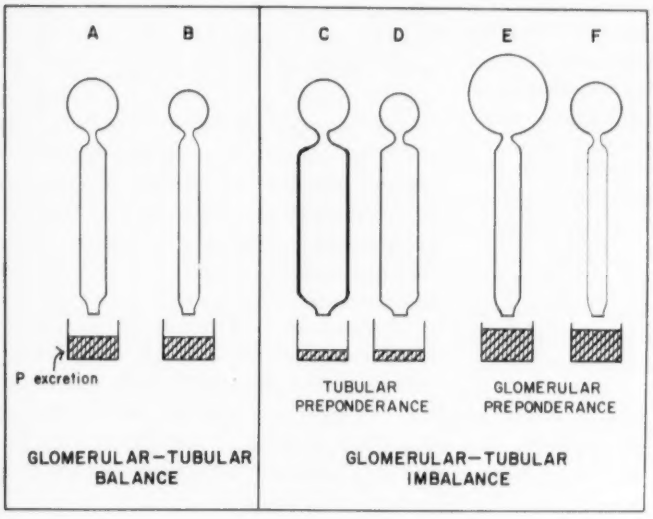

Fig. 2.—Schematic representation of glomerular-tubular balance and glomerular-tubular imbalance. The kidney is represented as a single nephron with a glomerulus and an attached tubule. Increases or decreases in glomerular function are illustrated by varying the size of the glomerulus. Changes in tubular activity are illustrated by varying the width of the tubule and the thickness of the tubular wall.

glomerular-tubular balance the term "glomerular function" includes both of these factors. Possible alterations in glomerular-tubular balance are illustrated in Figure 2, under the heading "glomerular-tubular imbalance." This category is divided into "tubular preponderance" and "glomerular preponderance." Tubular preponderance may result from an increase in tubular reabsorption associated with unchanged glomerular function (*C*) or may result from a combination of a constant tubular reabsorption in combination with reduced glomerular function (*D*). In either instance the net result is a reduction in phosphate excretion. Similarly, glomerular preponderance may result from augmented glomerular function together with unaltered tubular function (*E*) or unchanged glomerular function in association with reduced tubular function (*F*). The urinary phosphate excretion is increased above normal in these situations. If the amount of phosphate intake remains constant a reduction in excretion will result in a net accumulation of phosphate in the body and will be reflected in a rising plasma phosphate concentration. An increased phosphate excretion will result in a depletion of body phosphate and a reduction of plasma phosphate.

In normal human subjects glomerular filtration rate is very stable and is a relatively unimportant determinant of phosphate excretion. Tubular reabsorption of phosphate in normal subjects, however, varies widely from person to person and from time to time in any one person.[7] It is tempting to speculate that the variations represent adaptations of tubular function required to maintain phosphorus homeostasis. With increases in dietary phosphate intake the kidney responds by increasing its excretion. Increased excretion could result from (1) augmented glomerular function due principally to elevation of the plasma phosphate concentration, (2) a reduced tubular absorption by mechanisms to be discussed below, or (3) a combination of both effects. Studies have indicated that all of these possibilities may be seen.[29] In some normal subjects increased phosphate excretion is the result of an elevation of dietary phosphate intake or increased plasma phosphate, hence filtered phosphate, with little change in phosphate reabsorption. In other instances striking reductions in tubular reabsorption occur, and in some both factors are important. The nature of the response appears to be a function of time. Increased excretion initially, when dietary intake is increased, appears to be primarily the result of increased plasma phosphate concentration. With continuation of a high-phosphate intake tubular reabsorption falls, excretion increases, and the plasma phosphate returns toward normal.[15,29]

In renal disease reduction in filtration rate is common. In instances of slight to moderate reduction in GFR, tubular function may be depressed and glomerular-tubular balance remains (Fig. 2*B*). With further reduction in GFR, however, retention of phosphate occurs. The extent to which the plasma phosphate rises will depend not only on the extent of glomerular-tubular imbalance but also upon the dietary intake and the endogenous release of phosphate from body stores. In studies on patients with renal disease it has been found that the plasma phosphate concentration usually remains within the normal range until the GFR falls below 25 cc. per minute.[30] With severe impairment of GFR, the plasma phosphate will rise even though tubular reabsorption is negligible. In this situation, on a normal dietary phosphate intake, sufficient phosphate excretion to maintain balance can be achieved only by an elevation of plasma phosphate, even though there is a striking reduction in tubular reabsorption. Reduction of dietary phosphate intake and the oral administration of aluminum hydroxide gels, which bind phosphate and prevent its absorption from the intestine, will reduce the amount of phosphate which must be excreted by the kidney. Balance can then be achieved at a lower plasma phosphate level.

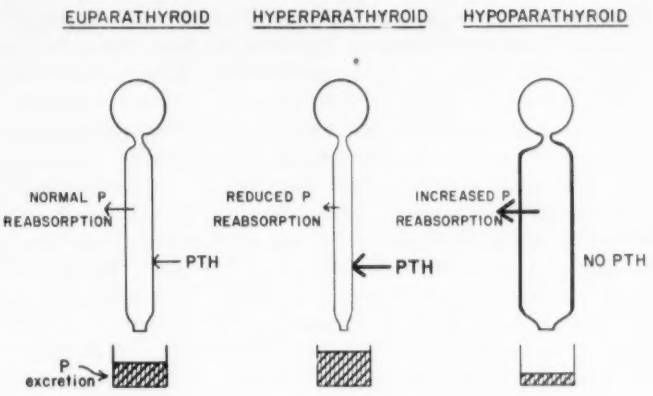

Fig. 3.—Activity of parathyroid hormone on renal reabsorption and excretion of phosphate. Glomerular preponderance due to depression of phosphate reabsorption is illustrated by the hyperparathyroid state. Tubular preponderance is illustrated by the hypoparathyroid state.

There is ample evidence that the tubular reabsorption of phosphate is modified by parathyroid hormone. Albright and associates concluded from studies on patients with hyperparathyroidism that the low plasma phosphate and the normal or elevated urinary phosphate excretion seen in these patients were the result of excessive amounts of parathyroid hormone acting upon the renal tubules to reduce phosphate reabsorption.[8] In this view, the high plasma phosphate and relatively low urine phosphate seen in hypoparathyroidism would be the result of overabsorption of phosphate by the renal tubules. There is now considerable evidence to support the thesis that the parathyroid hormone acts upon the renal tubules to reduce phosphate reabsorption.[9-11] In Figure 3 are illustrated the effects of varying amounts of parathyroid hormone on the renal tubular transport of phosphate.

It is probable that normal variations in urinary excretion of phosphate in part reflect fluctuations in the secretory activity of the parathyroid glands. If phosphate homeostasis is maintained by a simple feedback mechanism, parathyroid secretion should be regulated by the concentration of extracellular phosphate. It has been generally recognized that secretion of parathyroid hormone is influenced by the level of plasma calcium,[8,31] but there is some evidence to suggest that the level of serum phosphate is also important.[12-15] In long-standing renal disease parathyroid hyperplasia and hyperparathyroidism may occur in association with a chronically low plasma calcium and/or elevated plasma phosphate.

Adrenal cortical hormones also influence phosphate excretion. Cortisone administration results in phosphaturia, owing to diminished tubular reabsorption.[16] A similar response is seen when diethyl stilbestrol is administered to postmenopausal women, an effect thought to be due to suppression of growth hormone secretion.[34] Vitamin D in large doses has been shown to depress renal reabsorption of phosphate in parathyroidectomized animals.[17] This is one of the beneficial effects of vitamin D seen in hypoparathyroid patients.

The reabsorption of phosphate is influenced by the quantities of certain other substances transported by the proximal tubules. Glucose competes with phosphate, as indicated by the phosphaturia and depression of phosphate Tm seen after the infusion of dextrose.[4] Increased bicarbonate excretion brought about by the infusion of sodium bicarbonate or the administration of acetazolamide (Diamox) depresses phosphate Tm.[18] Acidosis increases phosphate excretion at normal plasma phosphate levels, although there is no reduction of phosphate Tm in man.[6] The increased phosphate excretion in acidosis is of importance, since phosphate is an effective urinary buffer.

The variability of phosphate excretion and tubular reabsorption is considerable.

A number of factors which are known to influence phosphate excretion have been mentioned. However, in many instances it is not possible to explain the fluctuations, and it is likely that additional factors will be identified which influence renal mechanisms concerned with phosphate excretion.

A number of syndromes have been described in which there is a relatively high phosphate excretion in association with a low serum phosphate.[19] These findings are the same as described for hyperparathyroidism and are indicative of a similar type of glomerular-tubular imbalance. In these diseases, however, there appears to be a congenital defect in the mechanism concerned with the renal tubular transport of phosphate, such that phosphate reabsorption is low. There are often additional defects, including deficient reabsorption of glucose and amino acids. Some of the syndromes in which impaired phosphate reabsorption has been noted are (1) vitamin D-resistant rickets, (2) Fanconi's syndrome, and (3) renal tubular acidosis. These diseases are most commonly recognized in children but have been described in adults.

Renal Excretion of Calcium

Although the intestine provides the main route for the elimination of calcium, abnormalities of calcium metabolism are often reflected in altered urinary excretion. The relationship between calcium excretion and calculus formation in the kidneys remains an important and poorly understood problem. There has been relatively little work done on the renal mechanisms controlling calcium excretion, in large part owing to the complex physicochemical state of calcium in plasma and urine.

As with phosphate, investigators have sought to define for calcium the renal processes of filtration, reabsorption, and excretion. The measurement of filtrable calcium is complicated because calcium exists in nonfiltrable and filtrable moieties in plasma. The nonfiltrable component is chiefly that calcium which is bound to circulatory albumin and represents about 40% of the total plasma calcium. The filtrable component, about 60% of the total, is mainly ionized calcium, although there is a small component complexed with the anions phosphate, sulfate, citrate, and perhaps others. In order to measure the filtered calcium it is necessary to perform carefully controlled ultrafiltration studies on plasma. Techniques are now available for this determination.[20]

Normally, less than 1% of the filtered calcium is excreted. When the plasma calcium is elevated there is increased excretion and also increased reabsorption. No maximal rate of calcium reabsorption, or Tm, is seen.[21] The relationship between filtered, excreted, and reabsorbed calcium at different levels of plasma calcium is indicated in Figure 4. Sodium and chloride ions behave in a similar fashion. It is probable that calcium, like sodium, is actively reab-

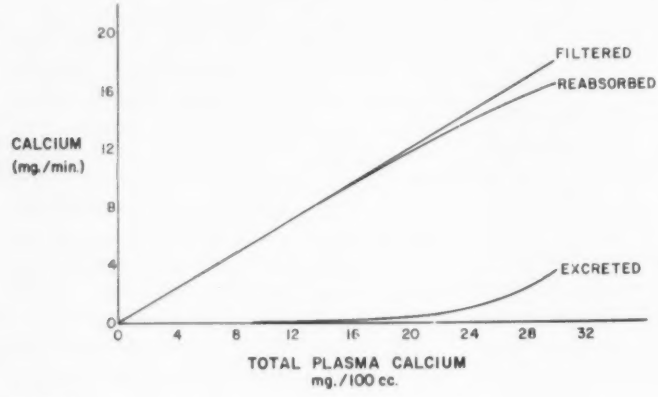

Fig. 4.—Normal relationship between the quantities of calcium filtered, excreted, and reabsorbed at various plasma calcium concentrations.

sorbed in the proximal tubules, but there is no clear-cut evidence of this.

Variations in calcium excretion in disease can often be correlated with the level of plasma calcium. In hyperparathyroidism the plasma concentration and the urinary excretion of calcium are characteristically elevated. In hypoparathyroidism the reverse is seen. Though excretion varies with the filtered load of calcium in these instances, it is also possible that alterations in tubular reabsorption may occur which would change excretion independently of the filtered load. Such changes in tubular reabsorption of other cations have been demonstrated. One example is the effect of aldosterone on sodium reabsorption. However, precise measurements are required to detect with certainty small fluctuations in tubular reabsorption. Some of the methodological problems which complicate such measurements for calcium have been mentioned.

The parathyroid hormone may act upon the renal tubules to increase calcium reabsorption. In acute studies parathyroidectomy in animals is followed by an immediate increase in calcium excretion, presumably the result of a decrease in calcium reabsorption. The administration of parathyroid extract in these animals results in a prompt reduction in calcium excretion.[22] Similar results have been found in human studies.[23] Thus, it appears that calcium excretion may be influenced by the level of plasma calcium, hence, filtered calcium, and by the effect of the parathyroid hormone on the tubular reabsorption mechanism.

Un-ionized but filtrable calcium salts are present in the tubular fluid. These compounds are poorly reabsorbed, if at all. Thus, reabsorption and excretion of calcium are also functions of the concentration of these un-ionized complexes. Infusions containing sulfate, phosphate, citrate, or the chelating agent edathamil (ethylenediaminetatraacetate) promote calcium excretion.[24,25] These compounds form poorly dissociated complexes with calcium and prevent its reabsorption.

The formation of calcium complexes, particularly calcium citrate, may be of importance in maintaining calcium in solution within the renal tubules. In rats, decreased citrate excretion in association with unchanged calcium and phosphorus excretion results in precipitation of calcium salts in the renal tubules.[26] These considerations may help shed light on the difficult problem of renal stone formation.[32]

Calcium ions have been shown to influence specifically the tubular reabsorption of other ions. The infusion of calcium gluconate in man results in a considerable increase in the urinary excretion of sodium, chloride, phosphate, and water.[27] In dogs, infusion of calcium gluconate and calcium chloride results in an increased excretion of sodium and magnesium.[28] The mechanism(s) by which calcium promotes the excretion of these other ions remains to be elucidated. The increased excretion of ions and water when the plasma calcium is elevated may explain the clinical observation of polyuria in association with hypercalcemia. It does not appear, however, that hypercalcemia is useful in producing a diuresis in clinical edematous states.[33]

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

The Advancement of Medical Research and Education Through the Department of Health, Education, and Welfare: Final Report of the Secretary's Consultants on Medical Research and Education. By S. Bayne-Jones, M.D., and committee. Price, not given. Pp. 82, with 19 tables and 6 charts. U. S. Government Printing Office, Washington, D. C., 1958.

Our country has not shown any recent signs of being wise and thoughtful in the long-term plans for the future. We have survived because we could react to the unexpected. So far we have made little serious attempt to bend the future to our desires or even to our needs. We are eternal improvisers. Such haphazard methods are nothing less than blueprints for disaster in a fast-paced world. To the end that we might proceed along more rational lines, Dr. Folsom, Secretary of the Department of Health, Education, and Welfare (what an incorrigibly hopeful paradox lies in his name), appointed a board of scrutiny to look into the crystal ball of the future as it gives glimmerings about the advancement of medical research and education. This is the future of medical research and education seen through the eyes of the National Institutes of Health. Dr. Bayne-Jones, who has had illustrious careers in diverse fields of medicine, gathered a group of distinguished colleagues, whose meditations and speculations have yielded this interesting document. Perhaps as a measure of the "audiovisual" time in which we live, they have used the figmentary quantum "gross national product," dear to the heart of the cliché mongers of business and advertising, as the standard to which just and honest men should repair. This is to guide our thinking not only about what we should spend to see that medical education and research keep up with all the spectacular advances which dazzle us but that we employ a high proportion of the available energy and brains of the nation to see that the fruits of science not only flourish but are plucked, eaten, and digested to nourish the fabric of the commonwealth. This vast problem is going into an exponential phase. Can we conserve quality while we produce quantity, since the mass production of an educated populous, summum bonum of a true democracy, has yet to be achieved? Those who have seen the great expansion of medical research enterprise since the end of World War II, with increasing governmental equity in supplying the where-with-all of lusty growth, have had misgivings lest the bounty of philanthropy, the fruits of endowment, the contributions of industry not only lose their proportionate role but wither under the philosophy of "let Uncle Sam do it."

If medical education and research need to be expanded and so require more money, what proportion of the "gross national product" should this be? What is a safe ratio of physician to the population, and should it be constant? Does the proliferating complexity of medicine, the vast stocks of data not digested into practical knowledge, require longer and different medical training or less training and for a shorter time? How can we anticipate the future in terms of reasonable probability?

From the first gleam in the eye of a university president or a potential dean to a fully operational hospital-medical school complex takes at least five to ten years. The assembling of a faculty, especially in those areas where scholars are not reproducing their kind, requires us to search out the reasons for the decline in numbers in the staff of preclinical sciences and the rare recruitment of those who have gone on to get the M.D. degree. Before we demand a sharp increase in the number of medical schools we should find ways to sustain a few which are drying up at the roots.

Those who love charts and numbers have extrapolated into the future the relative decline in physicians per 100,000 population and expect that, without a number of new medical schools, 1975 will see this reduced from 131.9 to 127.1. While not supposing that the eager breeders of our land will slacken off, it would behoove us to check promiscuous population growth, even let it decline, rather than just try to keep up with ungoverned torrent by the too rapid

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmissal to him.

manufacture of doctors. Those who saw the decline in quality in the wartime program of compressed training hope that there is more than one way for the "punishment to fit the crime."

Presumably longevity will not operate selectively in favor of physicians. Perhaps postgraduate education might enhance the effectiveness of physicians by five to ten per cent and thus eliminate the need for us to try to attain some static ratio of physician to population. Better quality, admittedly an elusive datum and one which statisticians have a hard time drawing on graphs or measuring for "significance," seems not to have suggested itself as a reasonable goal. Newer understanding of disease processes, the fruit of medical scholarship and research, has greatly increased the effectiveness of the well-trained physician even while it has increased the potential harm to be done by the doctor who has lost track of mechanisms and treats by rule of thumb according to the latest whim of advertising.

To what extent a reorientation of society, a frontal attack on the curious mass anxiety which besets us, might reduce the need for physicians or direct more of them into useful roles, rather than those which merely increase competitive uneasiness, is speculative. But difficult and uncertain thinking should not blind us to the fact that there are many roads to Rome, and none is downhill all the way. Perhaps even new roads are needed. Public health and scientific medicine have reduced the corporate anguish of epidemics, and going further might help make man healthier by being less self-centered and thus happier. These are heady hopes but not necessarily futile. Above all, they are never to be reached unless tried.

A more effective allocation of doctors is not likely to be reached without changing the whole face of society into a regimented mass organized at a low common demoninator. Thus the slight wastage of talent is the price we must pay to keep some freedom. Nonetheless, guidance must come from within medicine lest it be forced on us from outside, willy-nilly.

In short, the expansion of medicine must preserve excellence and must look to the objectives of full realization of each person by keeping the population from an explosive growth, which has been likened to a veritable cancer of the earth. We must find wisdom and foresight to keep the good name of medicine a shining beacon. Medical research and education, looking hopefully to a future, must hold excellence, not mass, and quality, not quantity, as the goals by which the future is to be used for the greater good of humanity, guided by human intelligence, and nurtured by the altruism which must continue to be the distinguishing mark of the man of medicine. Before we build twenty new medical schools which might be hollow shells, before we fix on a necessary fraction of the gross national product, we should question the frantic outburst of population growth and not fight fire with fire.

WILLIAM B. BEAN, M.D.

Principles of Research in Biology and Medicine. By Dwight J. Ingle, B.S., M.S., Ph.D. Price, $4.75. Pp. 123, with no illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1958.

If one reads critically much of what is written today in so-called scientific journals, he is forced to conclude that somewhere along the way instruction in many simple principles, which should have graced the training of an investigator, has been overlooked or skimped. Or, if it has been undertaken, too often it is of a slipshod kind which leaves the so-called scientific paper an awkward and grotesque skeleton for data, deformed by having few ideas to give it proper flesh and little style to make the telling of it pleasant. It rattles around in its bones, macabre and ghostly. The unwritten law of too many fabricators of research papers is that they must be dry and may be awkward. Some ancient guilt complex makes writers inflict some pain upon the reader, a retribution for the privilege of reading it.

Along broader lines than just writing, Dwight Ingle has confronted the problem of filling some of the gaps which so often leave the education of a scientist a sad parody on what the education of a scholar should be. To this end he has approached his subject in a simple and elementary way, as is befitting in an essay which proposes to get down to the first principles. Lending savor to the whole are many quotations from "Alice in Wonderland," which keep what might become pontifical and pompous always within range of the ironic. Lewis Carroll is a good touchstone by which to titrate the sense of the ridiculous which eases the burdens of those who take what pleasure they may from fun. This sense is deficient in those solemn small men whose brilliance has become tarnished by their overvaluation of their own personal uniqueness.

There is a clear introductory statement of the basic assumptions of science—the necessity for having a starting point in the acceptance of essential ideas. After all, everybody cannot prove everything that has ever been done all over again. The limitations of the mind of man

and the great subjective weight of bias in interpretation as well as in the choice of scientific objectives, a point about which the average layman seems to be utterly unaware, are justly emphasized in great detail. The whole problem of causality, the multiple nature of causes, and their complex interweaving and interrelationship are discussed simply but with emphasis. When one thinks of the remarkably few ways in which the internal and external environment can act upon a person to produce what we choose to call disease, we recognize the many faces of causality. The necessity to keep away from oversimplification in science becomes increasingly obvious and must be emphasized continually. And all these things, ideas, actions, and our accounts of them must be exchanged in words, whether they be written or spoken, for these are the symbols of communication, and they partake of the very process of thought itself, since we cannot think of thinking without symbols. These symbols are words and are better symbols than lines or numbers. Booby traps and road blocks are described in what, for the novice, must be a frightening degree of detail. But many have hardly thought of such things in fragments, much less *in extenso*.

The entire conception of normal comes in for critical discussion. The movement from the particular to the general and back to the particular, which must continue indefinitely as science provides clues for problems which then have to be tested, adds much to the interest of science. The complexity of man, the complexity of biology, and the great difficulties of scientific investigation and the principles on which these must rest, as well as the satisfactory design of experiments, Ingle develops as growing themes of interest. There are excellent words of advice about how to cut down, trim, and polish papers. One of the best features of the book is the essay on theory and its role in research. Then the finale deals with the transmission of ideas from teacher to pupil, from investigator to assistant and successor, and the vast complex organization of research. This is a wise little book which should be read and understood by all who undertake to do investigation in biology and medicine. Its disarming simplicity, its straightforward clarity, and its brief compass all conceal the excellent philosophy portrayed in it. It should take a place on the shelf beside Cannon's "Way of an Investigator," Dubos' "Life of Pasteur," Beverage's "The Art of Scientific Investigation," Thomas Lewis' "Clinical Science," Walsh's "Clinical Studies in Neurology," Claude Bernard's "Experimental Medicine," and a few other guides as a keenly analytical statement of those numerous elements of education for scientific research so often taken for granted and therefore so often forgotten completely.

WILLIAM B. BEAN, M.D.

Anatomies of Pain. By K. D. Keele, M.D., F.R.C.P. Price, $5.50. Pp. 215, with 27 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

In the present day, when analogies with mechanical and electronic models have obsessed the attention and preempted the enthusiasm of neurophysiologists, it is especially rewarding to go back to clinical observations and their long and sometimes tortuous history. The formidable title, "The Anatomies of Pain," seemed forbidding, and I wistfully looked at the book, which lay on the shelf for months before I managed to get it open. But when I did I found it thoroughly absorbing and well worth the wait. Essentially, this is a study of historical attitudes toward pain, with a description of our current-day formulations and understandings of the problem as these have emerged with our growing understanding of neurologic and emotional processes and reactions.

Pain cannot be understood detached from semantic, cultural, and emotional forces, even though we may know of essential neurophysiological mechanisms of the transmittal of electric current along paths of the nervous system and its arrival at the level of consciousness, with reflex or voluntary reactions expressed at various levels of integration. After a scholarly review of the history of ideas about pain, the volume concludes with a brilliant essay, essentially a review of the author's conception of pain, its mechanisms, and its medical importance, seen in the light of knowledge of the midtwentieth century. Typographical mistakes are rare, and punctuation is exemplary, with the exception of one statement, "This form of pain too often responds gratifyingly. . . ." There the "too" should certainly be segregated by commas. Those who look upon pain as a thing, a discrete essence rather than a process or reaction, will be disappointed in the deep probings which have enabled Keele to make this a wise, interesting, and illuminating book. Any physician would do well to study it carefully.

WILLIAM B. BEAN, M.D.

The Story Behind the Word. By Harry Wain, A.A., B.S.M., M.D., M.S.P.H. Price, $8.50. Pp. 340, with no illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

The fascination words hold is never-ending. The fascination of medical words for a physician has been the theme of many a discourse, paper, and book. Wain turned his hobby of collecting lore about medical terms into a full-time effort. He has selected from almost innumerable medical terms those of particular interest, to tell us something of their derivation, the fun which comes from knowing about how a word got that way, and a chatty little essay about the words he has selected. We might call to question the importance of putting contemporary physicians in a book of less than six thousand entries, particularly when the selection seems to have been based on whimsey or a lack of insight into the real contributions of some included and some excluded. But then, a book of this kind has to be selective anyhow, and no two people would choose alike. The work is pleasant and light, nothing very remarkable, but the impact of the whole indicates a vast amount of effort. It has some surprisingly useful as well as accurate information. One misses any comment about Sir Thomas Browne. There is no mention of Daniel Drake but instead a number of ephemeral medical people on the contemporary scene. *Pyorrhoca* retains the Greek diphthong, whereas *diarrhea* has lost it, but these are minor matters. It is up to date enough to contain *Orinase* and is full of choice little items about the origin of such words as *veronal, onion, paregoric,* and a great many others. This book, not in a class with Perry Pepper's book on medical etymology, does have some of the chatty, free-wheeling quality of the original Fowler. It is a ready reference book as well as being good for straight reading by those who subscribe to Osler's dictum that there is no literature like a dictionary and A. J. Knock's comment, "Considered as sheer casual reading matter, I still find the English dictionary the most interesting book in our language." Wain's book should be on the shelf of everyone who writes medical papers. It is a helpful guide for those who like to get an extra dividend out of what they read.

WILLIAM B. BEAN, M.D.

Liver-Brain Relationships. By Ian A. Brown, M.D., Ph.D. Price, not given. Pp. 198, with numerous illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

It is a great pity when a book with such a fascinating title as this turns out to be so carelessly written as to make one have grave doubts about some of the factual material contained in it. Any book so charged with error, confused writing, and all-pervasive awkwardness is a poor tribute to an author's capacity to achieve what are admittedly laudable aims. A warning of what is to come is found on the title page, in the hyphenation of Associate-Professor. We can only hope that the persons to whom the author renders thanks early in the book did not assume responsibility for the end-product.

The stated objective of the book is a worthy one. The case material and many of the tables are of much interest, approaching as they do an important but very abstruse problem in a field of very active research. But the writer has done himself a disservice by his failure to control the language in which the book is written. On a great many pages there were faults of spelling, syntax, or style. Proper names seemed to be just beyond the range of the author's visual field, and, lest he show favoritism, he spelled some of them wrong in different ways. Others he varied between the correct and the incorrect spelling. Cantabrigians may be startled to find that their university was once graced by a physician named "Glissonii." As a few examples of the obscure or erroneous expressions, we may cite the following ones.

In discussing the way he will use the word coma, the author says, "it does not include states in which coma is nonexistent."

"Throughout the years there has been a tendency to impute one substance as the cause of cerebral symptoms."

"The technician who records the sedimentation rate of the blood [is unable] to foretell the cause of an increased sedimentation rate."

"Infections . . . predispose to the . . . precipitation into coma."

". . . a polybiochemical hepatic disturbance underwrites the polysystemic cerebral involvement in hepatic coma."

"Two remaining factors that might mitigate against its use are the cost of the procedure [taking an electroencephalogram] and the fact that most interpretations in smaller institutions and hospitals are not done by electroencephalographic 'experts.' "

While the author very clearly recognizes that he has not discovered the secret of the numerous metabolic connections between brain and liver, it would be valuable to have a critical survey of what is known of these relationships. Unhappily, such is not to be found in this book.

WILLIAM B. BEAN, M.D.

Anatomist at Large. By George W. Corner, M.D. Price, $4. Pp. 215, with no illustrations. Basic Books, Inc., 59 4th Ave., New York 3, 1958.

George Corner's charming tale of his productive, friendly, and busy life, to which are added several delightful essays and speeches, makes up to a book full of stimulating reading for the physician. Renowned as investigator and teacher, he infuses more warmth into the printed page than most persons who have taken the opposite path from the laboratory to clinical medicine. One feels with him the thrill of discovery, the glowing satisfactions of a life of scholarship in teaching and investigation, and the personal love and loyalty he created for himself by his own warmth and charm. Those who wish to learn something of the personal anguish and medical problems of bladder stone almost two hundred years ago will find the tale of how "Benjamin Franklin Consults the Doctor" delightful.

A few minor carps, such as the use of "regime" for "regimen," the description of Heberden's nodes as a characteristic of rheumatoid arthritis, and the notion of the *destruction* of sugars by digestion, are trivial whisps, which a clinician may point out to a colleague in basic science. They simply underline the fact that the wonderfully human scholar and investigator who wrote this delightful book is not quite perfect. A book of this kind would be a real inspiration for those thinking of a career in medicine who want to know something of its mainly intangible rewards and for those whose curosity leads them into preclinical science, where creativity in research and the stimulus of graduate teaching offer rewards against which the more glamorous and prestige-conferring clinical fields have for too long carried the day. The transformation of an amateur historian into a professional is illustrated with many interesting sidelights. In the field of historical research in medicine as well as in laboratory investigation chance is an important factor, as illustrated in this book, but perhaps even more important is the fact that chance, or luck, can be converted into success only by the mind prepared. Corner's career illustrates this, and this charming book should inspire others to work as hard to reach a similar goal.

WILLIAM B. BEAN, M.D.

Heart Attack: New Hope, New Knowledge, New Life. By Myron Prinzmetal, M.D., and William Winter, Patient. Price, $3.50. Pp. 232, with no illustrations. Simon and Schuster, Inc., 136 W. 52d St., New York 19, 1958.

There is a flood of books about various diseases written for the instruction or comfort of the man at large. The layman or the patient may be expected to improve his mind or, oftener, to learn something of his own suspected or real medical problem. Many of these books serve a useful purpose, but their authors are confronted with the danger of oversimplification on the one hand or of explaining matters of irreducible complexity in terms that will make any sense to the nontechnically trained person. A negative aspect of many books for the layman is that they lead in the direction of neurosis. Some encourage too much of a devil-may-care, do-it-yourself attitude, which may cause trouble by causing the neglect of proper treatment. In an effort to circumvent some of these difficulties, Prinzmetal got help from a writer and television commentator, William Winter, who himself had suffered from a heart attack. First I read through this book trying to put myself in the place of a layman who was worried about his heart. This was too difficult. A number of things annoyed me. I resisted the patronizing attitude, forgetting that this is not a textbook and might not produce this kind of a reaction in a patient. Therefore, I gave the book to two different persons. One had had a heart attack, and one was apparently well. Neither was a physician. From both I got a strong indorsement of the matter as well as the manner of the book. Both believed that they had gotten new insights and valuable suggestions. Thus, what in a medical treatise would be slightly ectopic jocularity along with much oversimplification here has achieved the purpose of putting before the patient recovering from a heart attack enough information so that he can follow a therapeutic program intelligently. He avoids being mystified at what seem to him to be certain magic rituals which must be accomplished. He avoids the harrowing details which may foster a neurosis in addition to his other difficulty.

. I have no idea where may be the best way to heal the increasing breach between patient and physician, nor do I know how it will be possible for intelligent laymen to comprehend the increasing complexities of medicine or master the vast body of new and pertinent health data now growing by leaps and bounds in all directions. These have gotten beyond the competence of even the most assiduous individual physician. Nonetheless, books such as this serve a useful purpose if they can hew to the line of simple exposition of facts and avoid talking down to the reader or losing him in a morass of technical details.

Much sound sense and many helpful hints are found in the appendix, which deals with diet and includes a large number of menus. Cholesterol, the evil witch of our day, is exorcised and cast out, without forgetting that overindulgence in calories probably is the most important sin of our dietary habits.

WILLIAM B. BEAN, M.D.

Physics and Philosophy, the Revolution in Modern Science. By Werner Heisenberg. Price, $4. Pp. 206, with no illustrations. Harper & Brothers, 49 E. 33d St., New York 16, 1958.

I do not recall having met an educated person who claims to know less about contemporary physics than I do. Nevertheless, it has been my contention that as physicians living in the early part of the second half of the twentieth century we have very strong obligations to understand as much as we can of the world we live in. Perhaps if this could be done on a large scale events might be bent somewhat to wise purposes rather than just letting them happen. The introduction of the uncertainty principle, for which Heisenberg received the Nobel Prize, may be of some comfort in its oversimplified form as applied to research in biology. As I understand it, his essential belief is that by the very act of measuring a variable factor is introduced which disqualifies the evidence by virtue of altering the thing measured. Certainly, in clinical investigation and in biology generally, we often are forced to introduce artifacts into a system which will give us the opportunity for testing. Cutting off a butterfly's wings is no way to study the flight of the butterfly.

I picked up Heisenberg's book feeling bewildered by relativity, quantum theory, the fall of parity, and the extravagant destructive potential of an age in which someone in a temper tantrum might put us all out of business. I sought enlightment. Heisenberg's views here presented consist of a recent series of the Gifford lectures of the University of St. Andrew's. Thus they were of necessity nontechnical enough for a layman to form some judgment upon their matter.

Theoretical physicists, as they probe more deeply into the structure and motion of irreducibly small particles, have a goading urge to develop a unified theory which will subsume all knowledge of the operations of the physical world. Heisenberg is uneasy about what he considers to be incompatibilities between the theory of relativity and the quantum theory. To get at what he believes to be an essential universal constant in nature requires a unit of length, a unit of time, and a unit of mass, or, said another way, units of length, velocity, and energy. The velocity of light and Planck's constant of action give us only two of these units. Thus complete understanding is frustrated.

Much of the latter part of the book is devoted to an analysis of the relation of the quantum theory, its various interpretations, and its relevance to the structure of matter. Then in a detailed chapter, "Language and Reality in Modern Physics," we face the limitations imposed by symbolic representation of ideas. In the traditional culture in which we live, language has got to have certain basic but potentially changeable meanings. Physics and mathematics have a symbolism of their own. But despite the valiant efforts of the general semanticists to fix meanings and depend on precise definitions, words are never quite so easily definable as they seem to be on first sight. This puts finite limits on their effectiveness. But the other side of the coin is that science, be it biological or physical, has got to be based on language in order that ideas can be exchanged, and here, where precision is of supreme importance, we find ambiguity whether we will or no. For the physicist withdrawal into the more precise mathematical schemes of his constructs is possible, whereas for the biological scientist this is a long way off. As Heisenberg says, "We realize that the situation of complimentarity is not confined to the atomic world alone; we meet it when we reflect about a decision and the motives for our decision or when we have the choice between enjoying music and analyzing its structure. On the other hand, when the classical concepts are used in this manner, they always retain a certain vagueness, they acquire in relation to

their 'reality' only the same statistical significance as the concepts of classical thermodynamics in its statistical interpretation." The final chapter is an excellent summing up of his very stimulating views. The changing relationships of science and religion and the approach to metaphysics may make some physicists uneasy, but Heisenberg presents many interesting speculations. Though this book will not be an easy road to understanding atomic physics, it contains much to stimulate our mental activity and help us gain a better idea of the complexity of the physical world.

WILLIAM B. BEAN, M.D.

Our Nuclear Adventure, Its Possibilities and Perils. By D. G. Arnott. Price, $6. Pp. 176, with no illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1958.

Pollution of the earth, the air, and the sea is invented by scientists, managed by politicians, overlooked by the press, and imbued with immediate risk to the common man and will spell the fate of countless victims in future generations. Such is the view of this book, by a British nuclear technician, who writes "on the optimistic assumption that we are not going to be killed in a nuclear war."

Current planning estimates for a nuclear war "run in the order of several hundred million deaths," an American Senate committee was told in 1956. And the use of fission-fusion-fission bombs "on any appreciable scale in war," says Arnott, "would speedily render the whole planet untenable for all men."

But nuclear activity short of war, which is the real theme of this book, presents "a hazard some ten million times greater that that of any poison previously experienced by men." This hazard has two general sources and two modes of impact on the human race. One terrible source of hazard is in the testing of bombs, especially megaton bombs of the "dirty" fission-fusion-fission type. Arnott cites the Bikini explosion of March, 1954, which polluted seven thousand square miles of ocean and launched a stream of radioactive materials through ocean currents into the fishing fields of Japan, with disastrous impact on the Japanese food supply. Japan stands to suffer doubly from bomb-testing fall-out, from the United States when air movement is west and from Russia when it is east. But a comparable hazard, commonly overlooked, will come from the day-by-day routine handling of radioactive materials for constructive purposes, such as research and the production of power. One bright hope shines through these terrors. Nuclear activity as a source of power is becoming possible just when further progress of human civilization requires it. Britain already is making up for its shortage of coal by building reactors.

Radiation damage may be thought of first as somatic (affecting the present population) and genetic (affecting the future). In a present living body, if the damage is not too great the cells will repair it. Thus appears the concept of a threshold of safety. On the other hand, as with cancer, there may be a slight risk at any exposure, which may be calculated statistically as by an insurance mortality table. This is called the proportional concept. Genetic risk is more terrifying and uncalculable than somatic risk because it is cumulative and irreversible. The present generation never will know the outcome of its gamble, and future victims may never realize the causes of their troubles.

Crucial decisions in these matters are made by governments (politicians, Arnott calls them) over whom the people lack control. Control is lacking not only in Russia but in the United States and Britain. But he is not happy about prospects for control by business and industry, when distribution of isotopes and sale of reactors become responsibilities of managers who must weigh safety against profit at five per cent.

Arnott offers no cure-all, but an ultimate necessity is public opinion based on information. The necessary information is not too hard to understand but should be widely distributed. As a contribution Arnott offers his book, for which he has drawn heavily on Japanese, American, British, and other sources. He wishes every scientist could be induced to write one popular article or give one popular lecture each month. The popular press, he avers, offers little encouragement. It may be, however, that the newspapers and magazines of Britain and America and the rest of the free world will do better than Arnott hopes. Certainly the American press is doing its share to combat secrecy in government.

EDWARD F. MASON, M.A.

Tetany. By Hans Jesserer, M.D. Price, $7.10. Pp. 191, with 52 illustrations. Georg Thieme Verlag, Herdweg 63 (14a) Stuttgart N, 1958.

Vienna is still the "world capital of tetany." Consequently the author of this book has had the benefit of a large pool of patients afflicted with this disease and all its variations.

Dr. Jesserer has done much in the past and in his present publication to clarify the syndrome of tetany, which has been quite confused up to ten years ago.

The division of the clinical aspects of tetany into the hypocalcemic and normocalcemic forms is a logical one. So, in turn, is their subdivision into different groups based upon their pathological nature.

There are chapters especially dealing with tetany in infants, children, and juveniles; the relationship between tetany and other convulsive states, and the "formes frustes" of the tetanic syndrome.

The final chapter enumerates particularly interesting cases in which the author had to give his expert opinion in court.

The book is well written. The numerous illustrations are of good quality and instructive.

The bibliography (thirteen pages) is very extensive.

ENRICH STERN, M.D.

Correspondence

SARCOIDOSIS

To the Editor:—Since the publication of our study of 29 cases of sarcoidosis (A. M. A. ARCHIVES OF INTERNAL MEDICINE 101:1065-1084 [June] 1958) it has come to our attention that Patient 13, who was described in detail with splenic pancytopenia, died of a progressive, febrile, wasting illness. Necropsy revealed Hodgkin's disease. Review of the lymph node and spleen resected previously showed features compatible with atypical lymphoma exhibiting an unusual degree of fibrosis. This experience caused us to seek the available tissues in the other cases reported, and we were able to obtain slides in 18 of them. These were studied by two different pathologists, and the tissues were found to be histologically typical of sarcoidosis.

RICHARD H. FERGUSON, M.D.
JAIME PARIS, M.D.
Rochester, Minn.

News and Comment

ANNOUNCEMENTS

Nuclear Society Meeting.—The Sixth Annual Meeting of The Society of Nuclear Medicine will be held at the Palmer House, Chicago, on Thursday, Friday, and Saturday, June 18-20, 1959. Reservation forms for the Palmer House and a list of hotels and motels in the immediate vicinity will be mailed to the membership in approximately one month.

Additional information may be obtained by writing to Samuel N. Turiel, Administrator, The Society of Nuclear Medicine, 750 N. Michigan Ave., Chicago 11.

Civil Service Examinations.—Approximately 200 medical officers will be needed by the federal government this year for professional assignment in all of the specialized fields of medicine, the Civil Service Commission has announced. Experience requirements range from doctors who have just completed their internship to those who have had highly responsible professional experience. The positions are located throughout the United States and in foreign countries. Starting salaries range from $7,510 to $12,770 a year.

The major employers of medical officers in the federal government are the National Institutes of Health; Army, Navy, and Air Force Installations (civilian service); the Public Health Service; Indian Service Hospitals; the Food and Drug Administration; St. Elizabeth's Hospital, in the District of Columbia, and the Children's Bureau.

Federal Medical Officers have an opportunity to do research work in helping to maintain national health and to search for the causes of human diseases. They also care for patients in hospitals, clinics, military establishments, and other government organizations. The greatest need in these establishments has been in the fields of general medicine and surgery, nutrition, public health, tuberculosis, venereal disease, roentgenology, pathology, radiology, physical medicine and rehabilitation, and psychiatric medicine. Medical Officers serve as consultants in the administration of State medical programs, conduct programs and supervise medical personnel in industrial establishments which are under the direction of federal departments, or conduct health programs in a federal agency. They also make medical decisions which affect the enforcement of federal laws and claims for compensation on the basis of physical and mental disability and perform many other types of administrative work.

Doctors who desire further information regarding these positions should obtain a copy of Announcement No. 178 at a post office or from the U. S. Civil Service Commission, Washington 25, D. C. Applications will be accepted until further notice.

Fellowships in Human Ecology and Its Relation to Health.—A grant from the estate of Anne Parrish Titzell, Professor of Medicine (Neurology), Cornell University Medical College, has made possible the establishment of fellowships for those interested in the study of human ecology and its relation to health. An immediate purpose is to provide opportunities for study and investigation for men who plan to pursue academic careers. Three general areas are within the scope of the program: the investigation of the social and physical milieu in which men live and the attempt to learn more about how specific aspects of this milieu affect health and behavior; the investigation of the interaction between men and their milieu and of how a man's perception of his life situation influences his reaction to it; the investigation of the interaction between bodily processes and the highest integrative activities of the brain and the relevance of this to specific disease syndromes.

Dr. Lawrence E. Hinkle Jr. will be associated with Dr. Harold G. Wolff in the direction of the program. The staff of the human ecology study program includes representatives from the fields of internal medicine, psychiatry, neurology, psychology, sociology, and cultural anthropology. Fellows will have an opportunity to participate in field observations of groups drawn from the general population of "healthy people," to take part in the long-term observation and care of outpatients in a research facility especially designed for this purpose, and to make use of laboratory facilities for the study of behavior and of processes relating to the functions of various organ systems.

Three fellowship appointments will be made annually, each for a term of two years.

Applicants should have completed one or more years of postgraduate training in the fields of internal medicine, neurology, psychiatry, preventive medicine, or public health. The stipend allowed is $4,500 the first year and $5,000 the second; an additional allowance of $500 per annum is made for each dependent.

Those desiring to make application should write to Dr. E. Hugh Luckey, Chairman of the Department of Medicine, New York Hospital-Cornell Medical Center, 525 E. 68th St., New York 21.

International Society of Internal Medicine.—The Sixth International Congress for Internal Medicine will be held in Basel, Switzerland, from Aug. 24 to 27, 1960. This Congress will be organized in conjunction with the Swiss Society for Internal Medicine. For further details apply to the Secretariat of the Sixth International Congress for Internal Medicine, 13, Steinentorstr., Basel.

American Gastroscopic Society Meeting.—The 18th annual meeting of the American Gastroscopic Society will be held Sunday, June 7, at Haddon Hall in Atlantic City, N. J. Registration will be at 8:00 a. m. The program will include symposiums on Gastroscopic Color Photography, on Endoscopic Biopsy of the Stomach, and on Instruments and Techniques for Esophagoscopy. The following individual articles will be presented: "Gastroscopic Examination of the Terminal Esophagus and Esophagocardiac Junction"; "Management of Gastric Polyps"; "Clinical Manifestations of Extensive Atrophy of the Gastric Mucosa (Advanced Atrophic Gastritis)," and "Gastroscopic and Clinical Evaluation of Postgastrectomy Patients." The meeting will close with the Annual Banquet, at 7:30 p. m. At the banquet the Rudolph Schindler Award will be presented.

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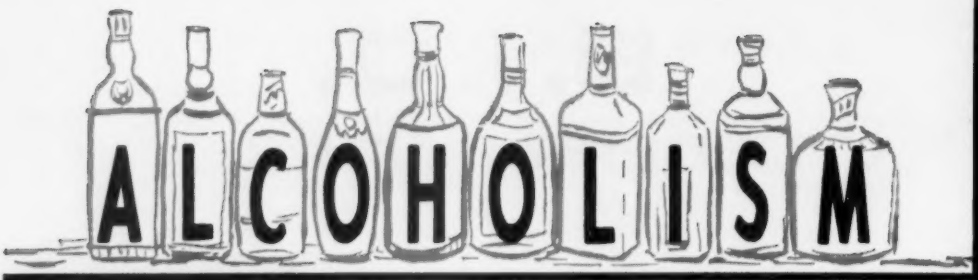

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BARBITURATES, BOOZE AND OBITUARIES. A discussion of the dangers of mixing alcohol and barbiturates. by Donald A. Dukelow, 4 pages, 10 cents.

TWELVE STEPS FOR ALCOHOLICS. A frank discussion of the meaning of an alcoholic behavior. by Richard Lake, 6 pages, 10 cents.

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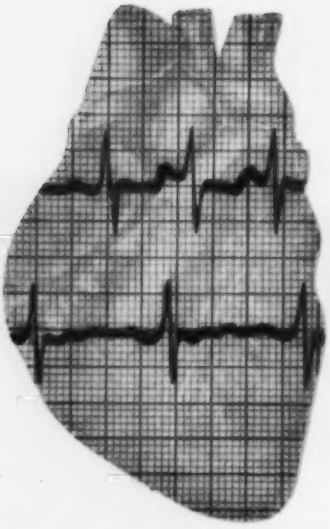

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1. Smith, J. M.: Lederle Bull. Symposium Report, 1:1, 1958.
2. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Internal Med. 100:750, 1957.

*Patent Applied For

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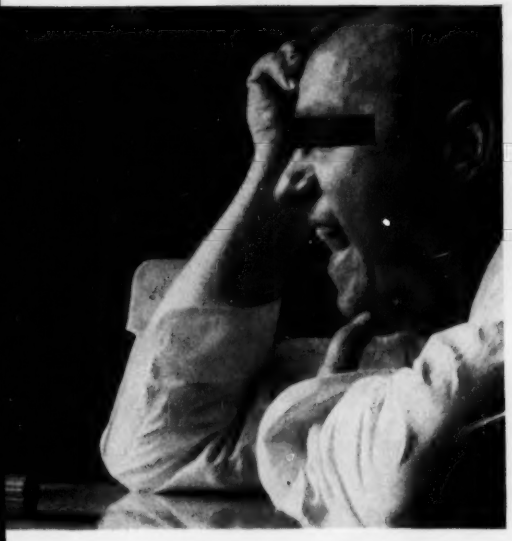


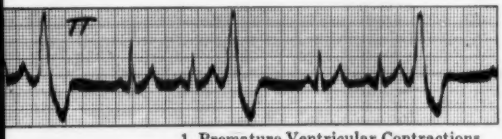
in alcoholism[1,2]

ACUTE EMERGENCIES—a single intramuscular injection of 50 mg. (2 cc.) Vistaril Parenteral Solution is usually sufficient to calm the patient and initiate sound sleep. Vistaril is exceptionally well tolerated. Antiemetic action and absence of respiratory depression are among valuable assets reported.

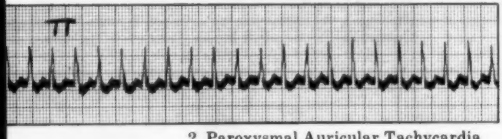
REHABILITATION—oral administration of 100-400 mg. daily in divided doses provides psychotherapeutic action which maintains calm and confidence, and promotes anxiety-free abstinence. The remarkable safety of Vistaril is reassuring in long-term maintenance.

VISTARIL

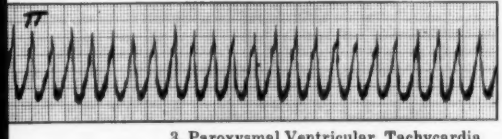
HYDROXYZINE PAMOATE



1. Premature Ventricular Contractions



2. Paroxysmal Auricular Tachycardia



3. Paroxysmal Ventricular Tachycardia

in arrhythmias[3,4]

Many types of cardiac arrhythmias respond promptly to oral, intramuscular or intravenous Vistaril therapy. Vistaril is particularly effective in ventricular extrasystoles, paroxysmal tachycardias (both auricular and ventricular), and ventricular extrasystoles complicating auricular fibrillation. The following dosage regimen is recommended:

PARENTERAL DOSAGE: 50-100 mg. (2-4 cc.) I.M. stat., and q. 4-6 h. p.r.n.; maintain with 25 mg. b.i.d. or t.i.d.

IN ACUTE EMERGENCY, 50-75 mg. (2-3 cc.) I.V. stat.; maintain with 25-50 mg. (1-2 cc.) I.V. q. 4-6 h. p.r.n.

ORAL DOSAGE: Initially, 100 mg. daily in divided doses until arrhythmia disappears. For maintenance or prophylaxis, 50-75 mg. daily in divided doses.

SUPPLY:
Vistaril Capsules, 25 mg., 50 mg. and 100 mg.
Vistaril Parenteral Solution, 10 cc. vials, and 2 cc. Steraject® Cartridges, each cc. containing 25 mg. hydroxyzine hydrochloride.

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REFERENCES: 1. Miller, R. F.: Clinical Review, Vol. 1, No. 2 (July) 1958. 2. Van Gasse, J. J.: Clinical Medicine, 5:177-181 (Feb.) 1958. 3. Burrell, Z. L., et al.: Am. J. Cardiol., 1:624 (May) 1958. 4. Hutcheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 118:451 (Dec.) 1956.

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Jordan and Grossman; Arch. Surg. 74: 871, 1957

Shingleton, et al; Surgery, 42: 12, 1957

Longmire, Jordan and Briggs; Ann. Surg. 144: 681, 1956

Krane; Am. Pract. and Digest, 8: 1275, 1957

Literature on request.

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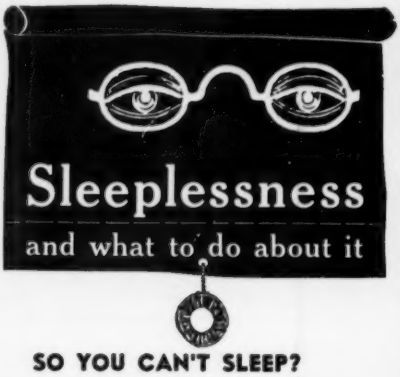

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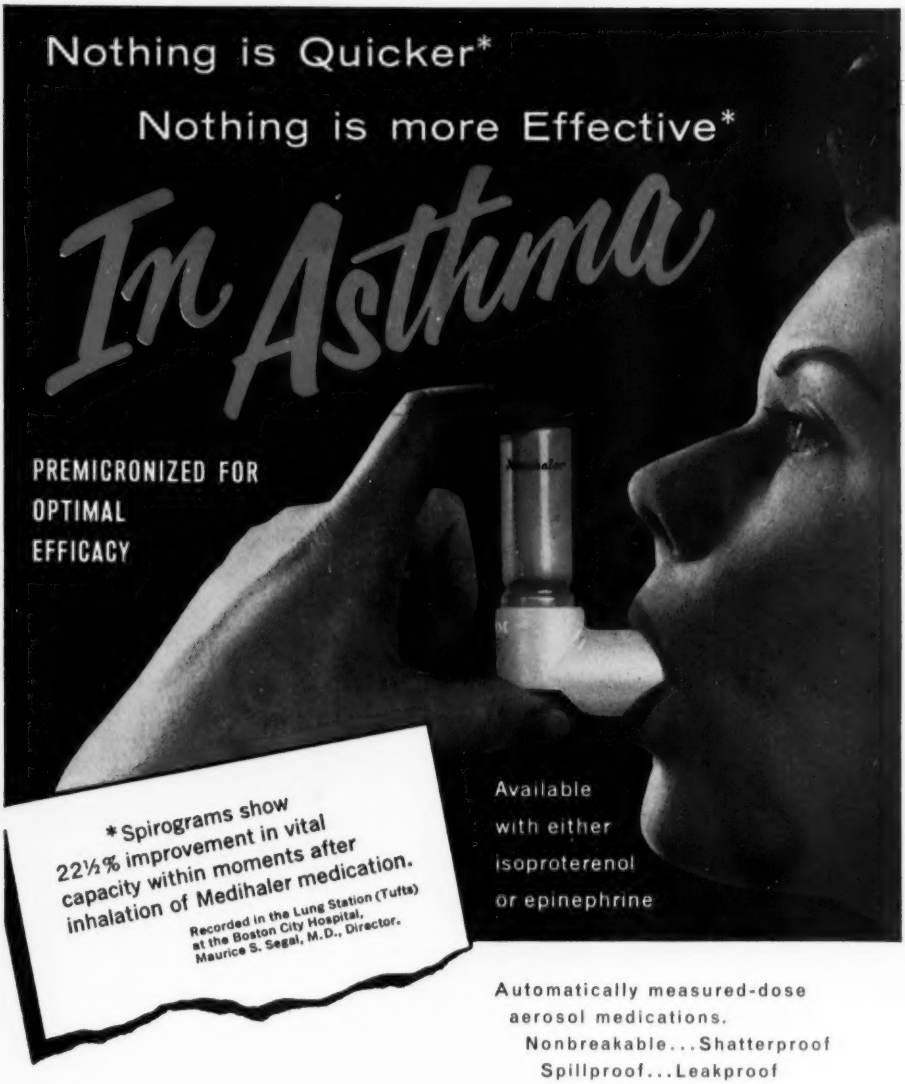
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